KINGDOM OF MOROCCO
MOHAMMED V UNIVERSITY OF RABAT
FACULTY OF MEDECINE
AND PHARMACY
RABAT

Year : 2021 **Thesis N°: 401**

CLINICAL AND CT SCAN FEATURES OF COVID-19 PATIENTS ADMITTED TO THE CENTER FOR VIROLOGY, INFECTIONS AND TROPICAL DISEASES ABOUT 186 CASES

THESIS

Publicly submitted and defended on the : / /2021

BY

Mrs. Yasmine MOUTMIR
Born on June 24th, 1996 in Paris
Intern doctor of University Hospital Center Rabat
From the Royal School of Military Health Service - Rabat

FOR THE DEGREE OF

Doctor of Medicine

Key Words : Covid-19; Clinicl features; CT scan features

Jury Members:

Mr. Hicham HARMOUCHE Professor of Internal Medicine	**President**
Mr. Khalid ENNIBI Professor of Internal Medicine	**Director**
Mr. Ahmed REGGAD Professor of Infectiology	**Member**
Mrs. Mouna MAAMAR Professor of Internal Medicine	**Member**
Mr. Youssef AKHOUAD Professor of Infectiology	**Member**

سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم

سورة البقرة: الآية: 31

UNIVERSITEMOHAMMEDV

FACULTE DE MEDECINE ET DE PHARMACIERABAT

DOYENS HONORAIRES :

1962 - 1969: Professeur Abdelmalek FARAJ
1969 - 1974: Professeur Abdellatif BERBICH
1974 - 1981: Professeur Bachir LAZRAK
1981 - 1989: Professeur Taieb CHKILI
1989 - 1997: Professeur Mohamed Tahar ALAOUI
1997 - 2003: Professeur Abdelmajid BELMAHI
2003 - 2013: Professeur Najia HAJJAJ - HASSOUNI

ADMINISTRATION :

Doyen :
Professeur Mohamed ADNAOUI
Vice-Doyen chargé des Affaires Académiques et estudiantines
Professeur Brahim LEKEHAL
Vice-Doyen chargé de la Recherche et de la Coopération
Professeur Taoufiq DAKKA
Vice-Doyen chargé des Affaires Spécifiques à la Pharmacie
Professeur Younes RAHALI

Secrétaire Général
Mr. Mohamed KARRA

1 - ENSEIGNANTS-CHERCHEURS MEDECINS ET PHARMACIENS
PROFESSEURS DE L'ENSEIGNEMENT SUPERIEUR :

Décembre 1984

Pr. MAAOUNI Abdelaziz	Médecine Interne-**Clinique Royale**
Pr. MAAZOUZI Ahmed Wajdi	Anesthésie -Réanimation
Pr. SETTAF Abdellatif	Pathologie Chirurgicale

Décembre 1989

Pr. ADNAOUI Mohamed	Médecine Interne –**Doyen de la FMPR**
Pr. OUAZZANI Taïbi Mohamed Réda	Neurologie

Janvier et Novembre 1990

Pr. KHARBACH Aîcha	Gynécologie -Obstétrique
Pr. TAZI Saoud Anas	Anesthésie Réanimation

Février Avril Juillet et Décembre 1991

Pr. AZZOUZI Abderrahim	Anesthésie Réanimation
Pr. BAYAHIA Rabéa	Néphrologie

Enseignant militaire

Pr. BELKOUCHI Abdelkader	Chirurgie Générale
Pr. BENSOUDA Yahia	Pharmacie galénique
Pr. BERRAHO Amina	Ophtalmologie
Pr. BEZAD Rachid	Gynécologie Obstétrique Méd. **Chef Maternité des Orangers**
Pr. CHERRAH Yahia	Pharmacologie
Pr. CHOKAIRI Omar	Histologie Embryologie
Pr. KHATTAB Mohamed	Pédiatrie
Pr. SOULAYMANI Rachida	Pharmacologie- **Dir. du Centre National PV Rabat**
Pr. TAOUFIK Jamal	Chimie thérapeutique

Décembre 1992

Pr. AHALLAT Mohamed	Chirurgie Générale **Doyen de FMPT**
Pr. BENSOUDA Adil	Anesthésie Réanimation
Pr. CHAHED OUAZZANI Laaziza	Gastro-Entérologie
Pr. CHRAIBI Chafiq	Gynécologie Obstétrique
Pr. EL OUAHABI Abdessamad	Neurochirurgie
Pr. FELLAT Rokaya	Cardiologie
Pr. JIDDANE Mohamed	Anatomie
Pr. ZOUHDI Mimoun	Microbiologie

Mars 1994

Pr. BENJAAFAR Noureddine	Radiothérapie
Pr. BEN RAIS Nozha	Biophysique
Pr. CAOUI Malika	Biophysique
Pr. CHRAIBI Abdelmjid	Endocrinologie et Maladies Métaboliques **Doyen de la FMPA**
Pr. EL AMRANI Sabah	Gynécologie Obstétrique
Pr. ERROUGANI Abdelkader	Chirurgie Générale – **Directeur du CHIS**
Pr. ESSAKALI Malika	Immunologie
Pr. ETTAYEBI Fouad	Chirurgie Pédiatrique
Pr. IFRINE Lahssan	Chirurgie Générale
Pr. RHRAB Brahim	Gynécologie –Obstétrique
Pr. SENOUCI Karima	Dermatologie

Enseignant militaire

Mars 1994

Pr. ABBAR Mohamed*	Urologie **Inspecteur du SSM**
Pr. BENTAHILA Abdelali	Pédiatrie
Pr. BERRADA Mohamed Saleh	Traumatologie – Orthopédie
Pr. CHERKAOUI Lalla Ouafae	Ophtalmologie
Pr. LAKHDAR Amina	Gynécologie Obstétrique
Pr. MOUANE Nezha	Pédiatrie

Mars 1995

Pr. ABOUQUAL Redouane	Réanimation Médicale
Pr. AMRAOUI Mohamed	Chirurgie Générale
Pr. BAIDADA Abdelaziz	Gynécologie Obstétrique
Pr. BARGACH Samir	Gynécologie Obstétrique
Pr. EL MESNAOUI Abbes	Chirurgie Générale
Pr. ESSAKALI HOUSSYNI Leila	Oto-Rhino-Laryngologie
Pr. IBEN ATTYA ANDALOUSSI Ahmed	Urologie
Pr. OUAZZANI CHAHDI Bahia	Ophtalmologie
Pr. SEFIANI Abdelaziz	Génétique
Pr. ZEGGWAGH Amine Ali	Réanimation Médicale

Décembre 1996

Pr. BELKACEM Rachid	Chirurgie Pédiatrie
Pr. BOULANOUAR Abdelkrim	Ophtalmologie
Pr. EL ALAMI EL FARICHA EL Hassan	Chirurgie Générale
Pr. GAOUZI Ahmed	Pédiatrie
Pr. OUZEDDOUN Naima	Néphrologie
Pr. ZBIR EL Mehdi*	Cardiologie **Directeur HMI Mohammed V**

Novembre 1997

Pr. ALAMI Mohamed Hassan	Gynécologie-Obstétrique
Pr. BIROUK Nazha	Neurologie
Pr. FELLAT Nadia	Cardiologie
Pr. KADDOURI Noureddine	Chirurgie Pédiatrique
Pr. KOUTANI Abdellatif	Urologie
Pr. LAHLOU Mohamed Khalid	Chirurgie Générale
Pr. MAHRAOUI CHAFIQ	Pédiatrie
Pr. TOUFIQ Jallal	Psychiatrie **Directeur Hôp.Ar-razi Salé**
Pr. YOUSFI MALKI Mounia	Gynécologie Obstétrique

Novembre 1998

Pr. BENOMAR ALI	Neurologie Doyen de la FMP Abulcassis
Pr. BOUGTAB Abdesslam	Chirurgie Générale
Pr. ER RIHANI Hassan	Oncologie Médicale
Pr. BENKIRANE Majid*	Hématologie

Janvier 2000

Pr. ABID Ahmed*	Pneumo-phtisiologie
Pr. AIT OUAMAR Hassan	Pédiatrie
Pr. BENJELLOUN Dakhama Badr Sououd	Pédiatrie

Enseignant militaire

Pr. BOURKADI Jamal-Eddine	Pneumo-phtisiologie
Pr. CHARIF CHEFCHAOUNI Al Montacer	Chirurgie Générale
Pr. ECHARRAB El Mahjoub	Chirurgie Générale
Pr. EL FTOUH Mustapha	Pneumo-phtisiologie
Pr. EL MOSTARCHID Brahim*	Neurochirurgie
Pr. TACHINANTE Rajae	Anesthésie-Réanimation
Pr. TAZI MEZALEK Zoubida	Médecine Interne

Novembre 2000

Pr. AIDI Saadia	Neurologie
Pr. AJANA Fatima Zohra	Gastro-Entérologie
Pr. BENAMR Said	Chirurgie Générale
Pr. CHERTI Mohammed	Cardiologie
Pr. ECH-CHERIF EL KETTANI Selma	Anesthésie-Réanimation
Pr. EL HASSANI Amine	Pédiatrie - **Directeur Hôp.Cheikh Zaid**
Pr. EL KHADER Khalid	Urologie
Pr. GHARBI Mohamed El Hassan	Endocrinologie et Maladies Métaboliques
Pr. MDAGHRI ALAOUI Asmae	Pédiatrie

Décembre 2001

Pr. BALKHI Hicham*	Anesthésie-Réanimation
Pr. BENABDELJLIL Maria	Neurologie
Pr. BENAMAR Loubna	Néphrologie
Pr. BENAMOR Jouda	Pneumo-phtisiologie
Pr. BENELBARHDADI Imane	Gastro-Entérologie
Pr. BENNANI Rajae	Cardiologie
Pr. BENOUACHANE Thami	Pédiatrie
Pr. BEZZA Ahmed*	Rhumatologie
Pr. BOUCHIKHI IDRISSI Med Larbi	Anatomie
Pr. BOUMDIN El Hassane*	Radiologie
Pr. CHAT Latifa	Radiologie
Pr. EL HIJRI Ahmed	Anesthésie-Réanimation
Pr. EL MAAQILI Moulay Rachid	Neuro-Chirurgie
Pr. EL MADHI Tarik	Chirurgie-**Pédiatrique Directeur Hôp. Des Enfants Rabat**
Pr. EL OUNANI Mohamed	Chirurgie Générale
Pr. ETTAIR Said	Pédiatrie - **Directeur Hôp. Univ. International (Cheikh Khalifa)**
Pr. GAZZAZ Miloudi*	Neuro-Chirurgie
Pr. HRORA Abdelmalek	Chirurgie Générale **Directeur Hôpital Ibn Sina**
Pr. KABIRI EL Hassane*	Chirurgie Thoracique
Pr. LAMRANI Moulay Omar	Traumatologie Orthopédie
Pr. LEKEHAL Brahim	Chirurgie Vasculaire Périphérique **V-D chargé Aff Acad. Est**.
Pr. MEDARHRI Jalil	Chirurgie Générale
Pr. MIKDAME Mohammed*	Hématologie Clinique
Pr. MOHSINE Raouf	Chirurgie Générale
Pr. NOUINI Yassine	Urologie
Pr. SABBAH Farid	Chirurgie Générale
Pr. SEFIANI Yasser	Chirurgie Vasculaire Périphérique
Pr. TAOUFIQ BENCHEKROUN Soumia	Pédiatrie

Enseignant militaire

Décembre 2002

Pr. AMEUR Ahmed *	Urologie
Pr. AMRI Rachida	Cardiologie
Pr. AOURARH Aziz*	Gastro-Entérologie
Pr. BAMOU Youssef *	Biochimie-Chimie
Pr. BELMEJDOUB Ghizlene*	Endocrinologie et Maladies Métaboliques
Pr. BENZEKRI Laila	Dermatologie
Pr. BENZZOUBEIR Nadia	Gastro-Entérologie
Pr. BERNOUSSI Zakiya	Anatomie Pathologique
Pr. CHOHO Abdelkrim *	Chirurgie Générale
Pr. CHKIRATE Bouchra	Pédiatrie
Pr. EL ALAMI EL Fellous Sidi Zouhair	Chirurgie Pédiatrique
Pr. FILALI ADIB Abdelhai	Gynécologie Obstétrique
Pr. HAJJI Zakia	Ophtalmologie
Pr. KRIOUILE Yamina	Pédiatrie
Pr. OUJILAL Abdelilah	Oto-Rhino-Laryngologie
Pr. RAISS Mohamed	Chirurgie Générale
Pr. SIAH Samir *	Anesthésie Réanimation
Pr. THIMOU Amal	Pédiatrie
Pr. ZENTAR Aziz*	Chirurgie Générale

Janvier 2004

Pr. ABDELLAH El Hassan	Ophtalmologie
Pr. AMRANI Mariam	Anatomie Pathologique
Pr. BENBOUZID Mohammed Anas	Oto-Rhino-Laryngologie
Pr. BENKIRANE Ahmed*	Gastro-Entérologie
Pr. BOULAADAS Malik	Stomatologie et Chirurgie Maxillo-faciale
Pr. BOURAZZA Ahmed*	Neurologie
Pr. CHAGAR Belkacem*	Traumatologie Orthopédie
Pr. CHERRADI Nadia	Anatomie Pathologique
Pr. EL FENNI Jamal*	Radiologie
Pr. EL HANCHI ZAKI	Gynécologie Obstétrique
Pr. EL KHORASSANI Mohamed	Pédiatrie
Pr. HACHI Hafid	Chirurgie Générale
Pr. JABOUIRIK Fatima	Pédiatrie
Pr. KHARMAZ Mohamed	Traumatologie Orthopédie
Pr. MOUGHIL Said	Chirurgie Cardio-Vasculaire
Pr. OUBAAZ Abdelbarre *	Ophtalmologie
Pr. TARIB Abdelilah*	Pharmacie Clinique
Pr. TIJAMI Fouad	Chirurgie Générale
Pr. ZARZUR Jamila	Cardiologie

Janvier 2005

Pr. ABBASSI Abdellah	Chirurgie Réparatrice et Plastique
Pr. AL KANDRY Sif Eddine*	Chirurgie Générale
Pr. ALLALI Fadoua	Rhumatologie
Pr. AMAZOUZI Abdellah	Ophtalmologie
Pr. BAHIRI Rachid	Rhumatologie **Directeur Hôp. Al Ayachi Salé**
Pr. BARKAT Amina	Pédiatrie

Enseignant militaire

Pr. BENYASS Aatif*	Cardiologie
Pr. DOUDOUH Abderrahim*	Biophysique
Pr. HAJJI Leila	Cardiologie (mise en disponibilité)
Pr. HESSISSEN Leila	Pédiatrie
Pr. JIDAL Mohamed*	Radiologie
Pr. LAAROUSSI Mohamed	Chirurgie Cardio-vasculaire
Pr. LYAGOUBI Mohammed	Parasitologie
Pr. SBIHI Souad	Histo-Embryologie Cytogénétique
Pr. ZERAIDI Najia	Gynécologie Obstétrique

Avril 2006

Pr. ACHEMLAL Lahsen*	Rhumatologie
Pr. BELMEKKI Abdelkader*	Hématologie
Pr. BENCHEIKH Razika	O.R.L
Pr. BOUHAFS Mohamed El Amine	Chirurgie - Pédiatrique
Pr. BOULAHYA Abdellatif*	Chirurgie Cardio – Vasculaire. **Directeur Hôpital Ibn Sina Marr.**
Pr. CHENGUETI ANSARI Anas	Gynécologie Obstétrique
Pr. DOGHMI Nawal	Cardiologie
Pr. FELLAT Ibtissam	Cardiologie
Pr. FAROUDY Mamoun	Anesthésie Réanimation
Pr. HARMOUCHE Hicham	Médecine Interne
Pr. IDRISS LAHLOU Amine*	Microbiologie
Pr. JROUNDI Laila	Radiologie
Pr. KARMOUNI Tariq	Urologie
Pr. KILI Amina	Pédiatrie
Pr. KISRA Hassan	Psychiatrie
Pr. KISRA Mounir	Chirurgie – Pédiatrique
Pr. LAATIRIS Abdelkader*	Pharmacie Galénique
Pr. LMIMOUNI Badreddine*	Parasitologie
Pr. MANSOURI Hamid*	Radiothérapie
Pr. OUANASS Abderrazzak	Psychiatrie
Pr. SAFI Soumaya*	Endocrinologie
Pr. SOUALHI Mouna	Pneumo – Phtisiologie
Pr. TELLAL Saida*	Biochimie
Pr. ZAHRAOUI Rachida	Pneumo – Phtisiologie

Octobre 2007

Pr. ABIDI Khalid	Réanimation médicale
Pr. ACHACHI Leila	Pneumo phtisiologie
Pr. AMHAJJI Larbi *	Traumatologie orthopédie
Pr. AOUFI Sarra	Parasitologie
Pr. BAITE Abdelouahed *	Anesthésie réanimation
Pr. BALOUCH Lhousaine *	Biochimie-chimie
Pr. BENZIANE Hamid *	Pharmacie clinique
Pr. BOUTIMZINE Nourdine	Ophtalmologie
Pr. CHERKAOUI Naoual *	Pharmacie galénique
Pr. EL BEKKALI Youssef *	Chirurgie cardio-vasculaire
Pr. EL ABSI Mohamed	Chirurgie générale
Pr. EL MOUSSAOUI Rachid	Anesthésie réanimation

Enseignant militaire

Pr. EL OMARI Fatima	Psychiatrie
Pr. GHARIB Noureddine	Chirurgie plastique et réparatrice
Pr. HADADI Khalid *	Radiothérapie
Pr. ICHOU Mohamed *	Oncologie médicale
Pr. ISMAILI Nadia	Dermatologie
Pr. KEBDANI Tayeb	Radiothérapie
Pr. LOUZI Lhoussain *	Microbiologie
Pr. MADANI Naoufel	Réanimation médicale
Pr. MARC Karima	Pneumo phtisiologie
Pr. MASRAR Azlarab	Hématologie biologique
Pr. OUZZIF Ez zohra *	Biochimie-chimie
Pr. SEFFAR Myriame	Microbiologie
Pr. SEKHSOKH Yessine *	Microbiologie
Pr. SIFAT Hassan *	Radiothérapie
Pr. TACHFOUTI Samira	Ophtalmologie
Pr. TAJDINE Mohammed Tariq*	Chirurgie générale
Pr. TANANE Mansour *	Traumatologie-orthopédie
Pr. TLIGUI Houssain	Parasitologie
Pr. TOUATI Zakia	Cardiologie

Mars 2009

Pr. ABOUZAHIR Ali *	Médecine interne
Pr. AGADR Aomar *	Pédiatrie
Pr. AIT ALI Abdelmounaim *	Chirurgie Générale
Pr. AKHADDAR Ali *	Neuro-chirurgie
Pr. ALLALI Nazik	Radiologie
Pr. AMINE Bouchra	Rhumatologie
Pr. ARKHA Yassir	Neuro-chirurgie **Directeur Hôp.des Spécialités**
Pr. BELYAMANI Lahcen *	Anesthésie Réanimation
Pr. BJIJOU Younes	Anatomie
Pr. BOUHSAIN Sanae *	Biochimie-chimie
Pr. BOUI Mohammed *	Dermatologie
Pr. BOUNAIM Ahmed *	Chirurgie Générale
Pr. BOUSSOUGA Mostapha *	Traumatologie-orthopédie
Pr. CHTATA Hassan Toufik *	Chirurgie Vasculaire Périphérique
Pr. DOGHMI Kamal *	Hématologie clinique
Pr. EL MALKI Hadj Omar	Chirurgie Générale
Pr. EL OUENNASS Mostapha*	Microbiologie
Pr. ENNIBI Khalid *	Médecine interne
Pr. FATHI Khalid	Gynécologie obstétrique
Pr. HASSIKOU Hasna *	Rhumatologie
Pr. KABBAJ Nawal	Gastro-entérologie
Pr. KABIRI Meryem	Pédiatrie
Pr. KARBOUBI Lamya	Pédiatrie
Pr. LAMSAOURI Jamal *	Chimie Thérapeutique
Pr. MARMADE Lahcen	Chirurgie Cardio-vasculaire
Pr. MESKINI Toufik	Pédiatrie
Pr. MESSAOUDI Nezha *	Hématologie biologique
Pr. MSSROURI Rahal	Chirurgie Générale

Enseignant militaire

Pr. NASSAR Ittimade	Radiologie
Pr. OUKERRAJ Latifa	Cardiologie
Pr. RHORFI Ismail Abderrahmani *	Pneumo-Phtisiologie

Octobre 2010

Pr. ALILOU Mustapha	Anesthésie réanimation
Pr. AMEZIANE Taoufiq*	Médecine Interne **Directeur ERSSM**
Pr. BELAGUID Abdelaziz	Physiologie
Pr. CHADLI Mariama*	Microbiologie
Pr. CHEMSI Mohamed*	Médecine Aéronautique
Pr. DAMI Abdellah*	Biochimie- Chimie
Pr. DARBI Abdellatif*	Radiologie
Pr. DENDANE Mohammed Anouar	Chirurgie Pédiatrique
Pr. EL HAFIDI Naima	Pédiatrie
Pr. EL KHARRAS Abdennasser*	Radiologie
Pr. EL MAZOUZ Samir	Chirurgie Plastique et Réparatrice
Pr. EL SAYEGH Hachem	Urologie
Pr. ERRABIH Ikram	Gastro-Entérologie
Pr. LAMALMI Najat	Anatomie Pathologique
Pr. MOSADIK Ahlam	Anesthésie Réanimation
Pr. MOUJAHID Mountassir*	Chirurgie Générale
Pr. ZOUAIDIA Fouad	Anatomie Pathologique

Decembre 2010

Pr.ZNATI Kaoutar	Anatomie Pathologique

Mai 2012

Pr. AMRANI Abdelouahed	Chirurgie pédiatrique
Pr. ABOUELALAA Khalil *	Anesthésie Réanimation
Pr. BENCHEBBA Driss *	Traumatologie-orthopédie
Pr. DRISSI Mohamed *	Anesthésie Réanimation
Pr. EL ALAOUI MHAMDI Mouna	Chirurgie Générale
Pr. EL OUAZZANI Hanane *	Pneumophtisiologie
Pr. ER-RAJI Mounir	Chirurgie Pédiatrique
Pr. JAHID Ahmed	Anatomie Pathologique

Février 2013

Pr.AHID Samir	Pharmacologie
Pr.AIT EL CADI Mina	Toxicologie
Pr.AMRANI HANCHI Laila	Gastro-Entérologie
Pr.AMOR Mourad	Anesthésie-Réanimation
Pr.AWAB Almahdi	Anesthésie-Réanimation
Pr.BELAYACHI Jihane	Réanimation Médicale
Pr.BELKHADIR Zakaria Houssain	Anesthésie-Réanimation
Pr.BENCHEKROUN Laila	Biochimie-Chimie
Pr.BENKIRANE Souad	Hématologie
Pr.BENSGHIR Mustapha *	Anesthésie Réanimation
Pr.BENYAHIA Mohammed *	Néphrologie
Pr.BOUATIA Mustapha	Chimie Analytique et Bromatologie

Enseignant militaire

Pr.BOUABID Ahmed Salim*	Traumatologie orthopédie
Pr BOUTARBOUCH Mahjouba	Anatomie
Pr.CHAIB Ali *	Cardiologie
Pr.DENDANE Tarek	Réanimation Médicale
Pr.DINI Nouzha *	Pédiatrie
Pr.ECH-CHERIF EL KETTANI Mohamed Ali	Anesthésie Réanimation
Pr.ECH-CHERIF EL KETTANI Najwa	Radiologie
Pr.ELFATEMI NIZARE	Neuro-chirurgie
Pr.EL GUERROUJ Hasnae	Médecine Nucléaire
Pr.EL HARTI Jaouad	Chimie Thérapeutique
Pr.EL JAOUDI Rachid *	Toxicologie
Pr.EL KABABRI Maria	Pédiatrie
Pr.EL KHANNOUSSI Basma	Anatomie Pathologique
Pr.EL KHLOUFI Samir	Anatomie
Pr.EL KORAICHI Alae	Anesthésie Réanimation
Pr.EN-NOUALI Hassane *	Radiologie
Pr.ERRGUIG Laila	Physiologie
Pr.FIKRI Meryem	Radiologie
Pr.GHFIR Imade	Médecine Nucléaire
Pr.IMANE Zineb	Pédiatrie
Pr.IRAQI Hind	Endocrinologie et maladies métaboliques
Pr.KABBAJ Hakima	Microbiologie
Pr.KADIRI Mohamed *	Psychiatrie
Pr.LATIB Rachida	Radiologie
Pr.MAAMAR Mouna Fatima Zahra	Médecine Interne
Pr.MEDDAH Bouchra	Pharmacologie
Pr.MELHAOUI Adyl	Neuro-chirurgie
Pr.MRABTI Hind	Oncologie Médicale
Pr.NEJJARI Rachid	Pharmacognosie
Pr.OUBEJJA Houda	Chirugie Pédiatrique
Pr.OUKABLI Mohamed *	Anatomie Pathologique
Pr.RAHALI Younes	Pharmacie Galénique **Vice-Doyen à la Pharmacie**
Pr.RATBI Ilham	Génétique
Pr.RAHMANI Mounia	Neurologie
Pr.REDA Karim *	Ophtalmologie
Pr.REGRAGUI Wafa	Neurologie
Pr.RKAIN Hanan	Physiologie
Pr.ROSTOM Samira	Rhumatologie
Pr.ROUAS Lamiaa	Anatomie Pathologique
Pr.ROUIBAA Fedoua *	Gastro-Entérologie
Pr SALIHOUN Mouna	Gastro-Entérologie
Pr.SAYAH Rochde	Chirurgie Cardio-Vasculaire
Pr.SEDDIK Hassan *	Gastro-Entérologie
Pr.ZERHOUNI Hicham	Chirurgie Pédiatrique
Pr.ZINE Ali *	Traumatologie Orthopédie

Enseignant militaire

Avril 2013

Pr.EL KHATIB MOHAMED KARIM *	Stomatologie et Chirurgie Maxillo-faciale

Mai 2013

Pr. BOUSLIMAN Yassir*	Toxicologie

Mars 2014

Pr. ACHIR Abdellah	Chirurgie Thoracique
Pr.BENCHAKROUN Mohammed *	Traumatologie- Orthopédie
Pr.BOUCHIKH Mohammed	Chirurgie Thoracique
Pr. EL KABBAJ Driss *	Néphrologie
Pr. EL MACHTANI IDRISSI Samira *	Biochimie-Chimie
Pr. HARDIZI Houyam	Histologie- Embryologie-Cytogénétique
Pr. HASSANI Amale *	Pédiatrie
Pr. HERRAK Laila	Pneumologie
Pr. JEAIDI Anass *	Hématologie Biologique
Pr. KOUACH Jaouad*	Gynécologie-Obstétrique
Pr. MAKRAM Sanaa *	Pharmacologie
Pr. RHISSASSI Mohamed Jaafar	CCV
Pr. SEKKACH Youssef*	Médecine Interne
Pr. TAZI MOUKHA Zakia	Gynécologie-Obstétrique

Décembre 2014

Pr. ABILKACEM Rachid*	Pédiatrie
Pr. AIT BOUGHIMA Fadila	Médecine Légale
Pr. BEKKALI Hicham *	Anesthésie-Réanimation
Pr. BENAZZOU Salma	Chirurgie Maxillo-Faciale
Pr. BOUABDELLAH Mounya	Biochimie-Chimie
Pr. BOUCHRIK Mourad*	Parasitologie
Pr. DERRAJI Soufiane*	Pharmacie Clinique
Pr. EL AYOUBI EL IDRISSI Ali	Anatomie
Pr. EL GHADBANE Abdedaim Hatim*	Anesthésie-Réanimation
Pr. EL MARJANY Mohammed*	Radiothérapie
Pr. FEJJAL Nawfal	Chirurgie Réparatrice et Plastique
Pr. JAHIDI Mohamed*	O.R.L
Pr. LAKHAL Zouhair*	Cardiologie
Pr. OUDGHIRI NEZHA	Anesthésie-Réanimation
Pr. RAMI Mohamed	Chirurgie Pédiatrique
Pr. SABIR Maria	Psychiatrie
Pr. SBAI IDRISSI Karim*	Médecine préventive, santé publique et Hyg.

Aout 2015

Pr. MEZIANE Meryem	Dermatologie
Pr. TAHIRI Latifa	Rhumatologie

Enseignant militaire

PROFESSEURS AGREGES :

Janvier 2016

Pr. BENKABBOU Amine	Chirurgie Générale
Pr. EL ASRI Fouad*	Ophtalmologie
Pr. ERRAMI Noureddine*	O.R.L
Pr. NITASSI Sophia	O.R.L

Juin 2017

Pr. ABI Rachid*	Microbiologie
Pr. ASFALOU Ilyasse*	Cardiologie
Pr. BOUAITI El Arbi*	Médecine préventive, santé publique et Hyg.
Pr. BOUTAYEB Saber	Oncologie Médicale
Pr. EL GHISSASSI Ibrahim	Oncologie Médicale
Pr. HAFIDI Jawad	Anatomie
Pr. MAJBAR Mohammed Anas	Chirurgie Générale
Pr. OURAINI Saloua*	O.R.L
Pr. RAZINE Rachid	Médecine préventive, santé publique et Hyg.
Pr. SOUADKA Amine	Chirurgie Générale
Pr. ZRARA Abdelhamid*	Immunologie

Mai 2018

Pr. AMMOURI Wafa	Médecine interne
Pr. BENTALHA Aziza	Anesthésie-Réanimation
Pr. EL AHMADI Brahim	Anesthésie-Réanimation
Pr. EL HARRECH Youness*	Urologie
Pr. EL KACEMI Hanan	Radiothérapie
Pr. EL MAJJAOUI Sanaa	Radiothérapie
Pr. FATIHI Jamal*	Médecine Interne
Pr. GHANNAM Abdel-Ilah	Anesthésie-Réanimation
Pr. JROUNDI Imane	Médecine préventive, santé publique et Hyg.
Pr. MOATASSIM BILLAH Nabil	Radiologie
Pr. TADILI Sidi Jawad	Anesthésie-Réanimation
Pr. TANZ Rachid*	Oncologie Médicale

Novembre 2018

Pr. AMELLAL Mina	Anatomie
Pr. SOULY Karim	Microbiologie
Pr. TAHRI Rajae	Histologie-Embryologie-Cytogénétique

Novembre 2019

Pr. AATIF Taoufiq*	Néphrologie
Pr. ACHBOUK Abdelhafid *	Chirurgie réparatrice et plastique
Pr. ANDALOUSSI SAGHIR Khalid	Radiothérapie
Pr. BABA HABIB Moulay Abdellah*	Gynécologie-Obstétrique
Pr. BASSIR RIDA ALLAH	Anatomie
Pr. BOUATTAR TARIK	Néphrologie
Pr. BOUFETTAL MONSEF	Anatomie
Pr. BOUCHENTOUF Sidi Mohammed *	Chirurgie-Générale
Pr. BOUZELMAT HICHAM *	Cardiologie

Enseignant militaire

Pr. BOUKHRIS JALAL *	Traumatologie-Orthopédie
Pr. CHAFRY BOUCHAIB *	Traumatologie-Orthopédie
Pr. CHAHDI HAFSA*	Anatomie pathologique
Pr. CHERIF EL ASRI ABAD *	Neuro-chirurgie
Pr. DAMIRI AMAL *	Anatomie Pathologique
Pr. DOGHMI NAWFAL*	Anesthésie-Réanimation
Pr. ELALAOUI SIDI-YASSIR	Pharmacie-Galénique
Pr. EL ANNAZ HICHAM*	Virologie
Pr. EL HASSANI MOULAY EL MEHDI*	Gynécologie-Obstétrique
Pr. EL HJOUJI ABDERRAHMAN *	Chirurgie Générale
Pr. EL KAOUI HAKIM *	Chirurgie Générale
Pr. EL WALI ABDERRAHMAN*	Anesthésie-Réanimation
Pr. EN-NAFAA ISSAM *	Radiologie
Pr. HAMAMA JALAL *	Stomatologie et Chirurgie Maxillo-faciale
Pr. HEMMAOUI BOUCHAIB*	O.R.L
Pr. HJIRA NAOUFAL *	Dermatologie
Pr. JIRA MOHAMED *	Médecine interne
Pr. JNIENE ASMAA	Physiologie
Pr. LARAQUI HICHAM *	Chirurgie-Générale
Pr. MAHFOUD TARIK *	Oncologie Médicale
Pr. MEZIANE MOHAMMED *	Anesthésie-Réanimation
Pr. MOUTAKI ALLAH YOUNES *	Chirurgie Cardio-Vasculaire
Pr. MOUZARI YASSINE *	Ophtalmologie
Pr. NAOUI HAFIDA *	Parasitologie-Mycologie
Pr. OBTEL MAJDOULINE	Médecine préventive, santé publique et Hyg.
Pr. OURRAI ABDELHAKIM *	Pédiatrie
Pr. SAOUAB RACHIDA *	Radiologie
Pr. SBITTI YASSIR *	Oncologie Médicale
Pr. ZADDOUG OMAR*	Traumatologie-Orthopédie
Pr. ZIDOUH SAAD *	Anesthésie-Réanimation

Enseignant militaire

2 - ENSEIGNANTS-CHERCHEURS SCIENTIFIQUE

PROFESSEURS DE L'ENSEIGNEMENT SUPERIEUR :

Pr. ABOUDRAR Saadia	Physiologie
Pr. ALAMI OUHABI Naima	Biochimie-chimie
Pr. ALAOUI KATIM	Pharmacologie
Pr. ALAOUI SLIMANI Lalla Naïma	Histologie-Embryologie
Pr. ANSAR M'hammed	Chimie Organique et Pharmacie Chimique
Pr .BARKIYOU Malika	Histologie-Embryologie
Pr. BOUHOUCHE Ahmed	Génétique Humaine
Pr. BOUKLOUZE Abdelaziz	Applications Pharmaceutiques
Pr. DAKKA Taoufiq	Physiologie **Vice-Doyen chargé de la Rech. et de la Coop**.
Pr. FAOUZI Moulay El Abbes	Pharmacologie
Pr. IBRAHIMI Azeddine	Biologie moléculaire/Biotechnologie
Pr. OULAD BOUYAHYA IDRISSI Med	Chimie Organique
Pr. RIDHA Ahlam	Chimie
Pr. TOUATI Driss	Pharmacognosie
Pr. ZAHIDI Ahmed	Pharmacologie

PROFESSEURS HABILITES :

Pr .BENZEID Hanane	Chimie
Pr. CHAHED OUAZZANI Lalla Chadia	Biochimie-chimie
Pr .DOUKKALI Anass	Chimie Analytique
Pr .EL JASTIMI Jamila	Chimie
Pr. KHANFRI Jamal Eddine	Histologie-Embryologie
Pr.LYAHYAI Jaber	Génétique
Pr. OUADGHIRI Mouna	Microbiologie et Biologie
Pr. RAMLI Youssef	Chimie
Pr. SERRAGUI Samira	Pharmacologie
Pr. TAZI Ahnini	Génétique
Pr. YAGOUBI Maamar	Eau, Environnement

Mise à jour le 09/04/2021
KHALED Abdellah
Chef du Service des Ressources Humaines
FMPR

****Enseignant militaire***

Dedications

TO

HIS LATE MAJESTY THE KING

HASSAN II

May God have his soul in his Holy Mercy.

TO

HIS MAJESTY THE KING MOHAMMED VI

SUPREME LEADER AND CHIEF OF GENERAL STAFF OF THE ROYAL ARMED FORCES

KING OF MOROCCO AND GUARANTOR OF ITS TERRITORIAL INTEGRITY

May Allah glorify him and preserve his Kingdom

TO

HIS ROYAL HIGHNESS CROWN

PRINCE MOULAY EL HASSAN

May God protect him

TO

HIS ROYAL HIGHNESS PRINCE

MOULAY RACHID

May God protect him

TO THE ENTIRE ROYAL FAMILY

To

Monsieur le Général de Corps d'Armée
Belkhir EL FAROUK
Inspecteur Général des Forces Armées Royales

As a token of our great respect
And our deep consideration

To
Monsieur le Médecin Général de Brigade
Mohammed ABBAR
Inspecteur du Service de Santé Militaire

As a token of our great respect
And our deep consideration

To

Monsieur le Médecin Général de Brigade

El Mehdi ZBIR

Directeur de l'Hôpital Militaire d'Instruction

Mohamed V - Rabat

As a token of our great respect,

And our deep consideration and sincere admiration

To

Monsieur le Médecin Général de Brigade

BOULAHYA Abdellatif

Directeur de l'Hôpital Militaire Avicenne - Marrakech

As a token of our great respect

And our deep consideration

To

Monsieur le Colonel Major

Abderrazak SABIR

Médecin Chef du 3ème Hôpital de Laayoune

As a token of our great respect

And our deep consideration

To

Monsieur le Médecin Colonel Major

Karim FILALI

Directeur de l'Ecole Royale du Service

de Santé Militaire

As a token of our great respect

And our deep consideration

To

Monsieur le Médecin Colonel Major

Mohammed El Baaj

Directeur de l'Hôpital Militaire Moulay Ismail - Meknès

As a token of our great respect

And our deep consideration

To my dad. I have been looking up to you since I was a little girl.
Your dedication, your principles, your straightness, and your
rigor always inspired me. You are a role model, and
a great source of admiration.
I dedicate my work to you, hoping that it rises to your expectations,
and that it pays back at least a tiny part of all the
fights and sacrifices you made.
I hope that you are proud of the doctor I've become.

To my mom. You have always been by my side, loving, cheering,
and taking care of me, even when I was capricious and stubborn.
All the things of the world can't pay you back for
all the sacrifices you made.
And by dedicating this work to you, I wish to
make you happy and proud of me.

To Zyad. My confident, my best friend. You sure are my little brother, but you've always acted like the big one.
We share everything together. But today you are not here, which makes me sad and happy for you at the same time.
I'm very proud of you.
I miss you so much Zizou, and hope to see you soon.

To Layla. My partner in crime "laban", my little sweet -not so sweet- sister, I love you so much.
You shared with me my darkest times, and your support made me stronger and helped me through it all.
I am proud of the strong young woman you've become, although I still can't believe how fast you grew up!
I'll always be there for you, I got ya man!

To Amine. My husband, the love of my life. I will never thank you enough for all the love, the support, the time (that you so don't have) you're offering me.
You make me the happiest. I love you to the moon, the Milky Way and beyond babes, and I'm proud of what we've become.
I hope I'm making you proud as well.

To my family.
To my late grandfathers and my grandmothers, and to my aunts and uncles.
I dedicate my work to you, and I'm grateful for your love and support.

To Samia. My bestie “Sousou”, or should I say my sister.
You’re the most wonderful person I’ve ever known.
You can’t imagine how much you mean to me, and
how much I’m grateful to have you in my life,
(although I remind you of that quite often).
Your presence, you support and your wise advices are the best
things a person can get. I wove you hani.

To Hatim. Mon Lieutenant. No matter what your rank is,
you will remain my best friend.
You are so precious to me, even within your “extension” phases.
You can be stubborn, sometimes annoying, and even stupid,
but our friendship will always overcome all
this, because I love you buddy.
PS: Tap here to translate.

To the best interns. Class of 2020.
Marouane, Sarah, Karima, Sofia, Imad, Ayman,
Reda, Bilal, Samah, Raihana, Maryeme.
Thank you for making these internship years special.

To all my friend and colleagues.

To the medical officer cadets of ERSSM, class of 2013.

To all those who have contributed in any way to this work.

And to all those I have omitted to mention.

Acknowledgments

To Professor

HARMOUCHE HICHAM

You do me the honor of chairing the jury of this thesis.

Please find here the expression of my deep esteem and warmest gratitude.

To Professor

ENNIBI Khalid

It is such a great honor to have you as the director of my thesis.

I am sincerely grateful for your support, and for your time, that I know how hard it was to find, especially during this conjuncture.

You allowed me to surpass myself, while ensuring me a good guidance, and I really appreciated my time working in your department.

To Professor

MAAMAR Mouna

Your kindness of accepting to be part of committee members in this thesis is greatly appreciated.

To Professor

REGGAD Ahmed

You do me the honor of judging this work, please find here the expression of my sincere acknowledgments and my deepest respect.

Your accuracy and your valuable advice were constructive and very helpful.

To Professor

AKHOUAD Youssef

I owe you my deepest gratitude for accepting to judge this thesis and to be a part of committee members.

Working with you has been a great honor
and a source of inspiration.

Abbreviations

ABREVIATIONS

ACE2 : Angiotensin converting enzyme 2

ACR : the American College of Radiology

AgPOCT : Point-of-care antigen test

AIDS : Acquired immune deficiency syndrome

Ang II : Angiotensin II

ARDS : Acute respiratory distress syndrome

AT1R : Angiotensin II type 1 receptor

CBC : Cell blood count

CO-RADS : COVID-19 Reporting and Data System

COVID-19 : Coronavirus Disease 2019

CRP : C-reactive protein

CRRT : Continuous renal replacement therapy

CT : Computed tomography

CV MIT : Center for Virology and Infectious and Tropical Diseases

DPP4 : Dipeptidyl peptidase 4

ECMO : Extracorporeal membrane oxygenation

FGF : Fibroblast growth factor

FIP : Feline Infectious Peritonitis

G-CSF : Granulocyte colony-stimulating factor

GGO : Ground glass opacity

GM1 : Mono-sialo-tetrahexosyl-ganglioside

GM-CSF : Granulocyte-macrophage colony stimulating factor

HCoVs : Human coronaviruses

HE : Hemagglutinin-esterase

IBV : Infectious bronchitis virus

ICU : Intensive care unit

IDU : Infectious disease unit

IFN gamma : Interferon gamma

IP10 : Interferon induced protein-10

IVIg : Intravenous immunoglobulin

KDIGO : Kidney Disease: Improving Global Outcomes

LDH : Lactate Dehydrogenase

LMWH : Low molecular weight heparin

LOD : Limit of Detection

Mas : Monoclonal antibodies

MCP-1 : Monocyte chemoattractant protein-1

MERS : Middle East respiratory syndrome

MHV : Mouse hepatitis virus

MIP1A : Macrophage inflammatory protein 1Alpha

NAATs : Nucleic acid amplification tests

NEWS : National Early Warning Score

NSPs : Nonstructural proteins

PA : Posteroanterior

PCR : Polymerase chain reaction

PDGF : Platelet derived growth factor

PLR : Platelet-to-lymphocyte ratio

PPE : Personal protective equipment

Qpcr : Quantitative PCR

RdRp : RNA-dependent RNA polymerase

RSNA : Radiological Society of North America

RT-PCR : Reverse transcription polymerase chain reaction

SARS : Severe acute respiratory syndrome

SARS-CoV-2 : Severe acute respiratory syndrome coronavirus 2

SERAM : Spanish Association of Medical Radiology

SPSS : Statistical Package for the Social Sciences

TMPRSS2 : Transmembrane serine protease

TNF alpha : Tumor necrosis factor alpha

UTR : Untranslated region

VEGF : Vascular endothelial growth factor

WHO : World Health Organization

LIST OF FIGURES

LIST OF TABLES

Summary

SUMMARY

Introduction

In December 2019, the city of Wuhan, located in the Hubei province of China, became the epicenter of an outbreak of a pneumonia of unknown cause, with a high potential of transmissibility between humans. **[1]**

The Chinese Center for Disease Control and Prevention, along with other related institutions, quickly identified the pathogen as a new type of coronavirus (2019-nCOV).

World Health Organization (WHO) issued alerts on December 30, 2019, and on January 30, 2020, declared this viral infection as a Public Health Emergency of International Concern. On February 11, 2020, the International Committee of Taxonomy of Viruses named this virus severe acute respiratory syndrome (SARS)-CoV-2 based on the phylogenetic relationship of the coronavirus that caused the SARS outbreak in 2003 **[2]**. On the same day, WHO announced COVID-19 as the name of this novel disease caused by this virus, and COVID-19 viral disease was declared officially a pandemic, by WHO Director-General Tedros Adhanom Ghebreyesus in Geneva on March 11, 2020 **[3].**

In Morocco, the COVID-19 pandemic situation is far from stable. The virus was confirmed to have spread to Morocco on March 2, 2020, when the first COVID-19 case was confirmed in Casablanca. It involved a Moroccan expatriate residing in Bergamo, Italy, who arrived from Italy on February 27.
A second case was confirmed later that same day, involving an 89-year-old woman Moroccan residing in Italy who had returned to Morocco on February 25 from Bologna, Italy **[4].** As the outbreak widened in Morocco, in mid-March the Government closed schools and suspended international passenger flights. And by March 20, 2020, the general containment was declared on a national scale, to control the introduction of cases into the country, delay the circulation of the virus, and contain the outbreak of the disease.

As of February 1st, 2021, 13 to 14 months after the first description of the virus, there are over 100 million subjects globally (from more than 210 countries) with confirmed SARS-CoV-2 infection based on the molecular assay. More than 2 million deaths have been attributed to COVID-19 **[5]**.
This pandemic has posed a great menace to human physical and mental health, and has dramatically impacted the daily life with psychosocial implications on a global scale **[2]**.
Currently, by December 2021, there have been 268,226,835 confirmed cases, of which 241,432,735 have recovered and 5,298,095 have died **[3]**, and the pandemic is still raging on.
COVID-19 is a benign disease in 80% of cases, and in about 10 to 20% of cases, particularly in elderly subjects or those with comorbidities, the clinical picture can be more severe, requiring specific management.
It presents with a diverse and sometimes misleading symptomatology, and may result in death in 2% of cases.
There is limited published data on the clinical and morphological features predictive of a progression to severity or death.

The aim of our study is to:

- Describe the clinical, biological and morphological presentation of the first cases admitted and treated at the beginning of the pandemic.
- Establish a possible correlation between the clinical and morphological features on CT scan.
- Define the predictive factors of an unfavorable outcome.

Reminder

I. HISTORY

The first coronaviruses isolated were from poultry with respiratory disease (infectious bronchitis) in the 1930s. The infectious bronchitis virus (IBV) is a gamma coronavirus that causes a highly contagious disease in chickens. The virus can affect the upper respiratory tract and the reproductive tract, and some strains can cause a nephritis. It remains a worldwide problem, particularly in high-density commercial production facilities **[6]**.

But it seems that coronaviruses (or a virus interacting similarly with hosts) have driven ancient epidemics in East Asia over 20,000 years ago. Recent research applying evolutionary analyses to human genomic datasets found that a strong genetic adaptation occurred in human East Asian populations, at multiple genes that interact with coronaviruses, including SARS-CoV-2. The adaptation likely started 25,000 years ago, and functional analysis of the adapting genes supports the occurrence of a corona- or related virus, epidemic around that time in East Asia **[7]**.

Until 2002, human coronaviruses (HCoVs) were associated only with mild respiratory tract disease, with estimates that they caused 15%-25% of all "common colds."

Since then, coronaviruses have been behind three major zoonotic outbreaks.

In 2002, a human coronavirus was identified as the cause of an apparently new disease called severe acute respiratory syndrome (SARS), which is a viral respiratory disease caused by a SARS-associated beta-coronavirus. It was first identified at the end of November 2002 during an outbreak that emerged in China, and characterized epidemic on February 2003.

SARS is an airborne virus and can spread through small droplets of saliva in a similar way to the cold and influenza, and can also spread indirectly via surfaces that have been touched by someone who is infected with the virus.

It was the first severe and readily transmissible new disease to emerge in the 21st century and showed a clear capacity to spread along the routes of international air travel **[3]**.

It eventually spread to 37 countries around the world. The total number of confirmed cases was 8096 and the average fatality rate close to 10% **[8]**.

The SARS outbreak was controlled, but a decade later, in 2012, another novel CoV was isolated from patients hospitalized with severe respiratory disease in Saudi Arabia. As most infected patients lived in or had traveled to Middle East countries, the new disease was named MERS and the coronavirus responsible is called HCoV-MERS, **[6]** with cases of illness spreading sporadically to other countries. Since September 2012, about 1791 cases were confirmed with an average fatality of 30%. The source of MERS-CoV is not fully understood, but genomic studies suggest an original reservoir in bats that was possibly later extended to include camels **[9]**.

More recently, at the end of December 2019, an outbreak of mysterious pneumonia occurred in Wuhan City, China. It was observed that the etiologic agent of the disease was a novel CoV, previously designated 2019-nCoV by WHO and later, SARS-CoV-2 by the International Committee for Taxonomy of Viruses.

Consequently, China has been the epicenter of the emergence of the disease called COVID-19 (Coronavirus disease 2019), responsible of an ongoing pandemic **[10]**.

II. EPIDEMIOLOGY

A. Infectious agent

Members of the family Coronaviridae are large, enveloped, single-stranded RNA viruses. They are the largest known RNA viruses, with genomes ranging from 25 to 32 kb and a virion of 118-136 nm in diameter. Virions are roughly spherical and are notable for the large spike (S) glycoprotein that extends 16-21nm from the virus envelope (*Figure 1*) **[6]**.

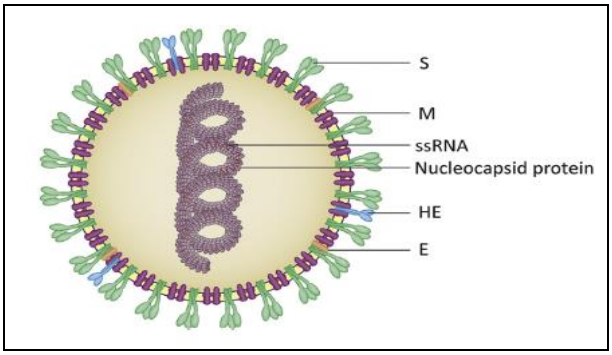


Figure 1: *Virion structure (subfamily Coronavirinae)* **[6]**.

The family contains two subfamilies, the Coronavirinae and the Torovirinae (*Figure 2*) (detailed in Appendix *Table 1*) **[6]**.

Family	*Coronaviridae*
Subfamily	*Coronovirinae*
Genus	*Alphacoronavirus*
Genus	*Betacoronavirus*
Genus	*Deltacoronavirus*
Genus	*Gammacoronavirus*
Subfamily	*Torovirinae*
Genus	*Torovirus*
Genus	*Bafinivirus*

Figure 2: *Taxonomic structure of the family* **[6]**.

The toroviruses are notable for having a helical, doughnut shaped nucleocapsid. (*Figure 3*) **[6]**.

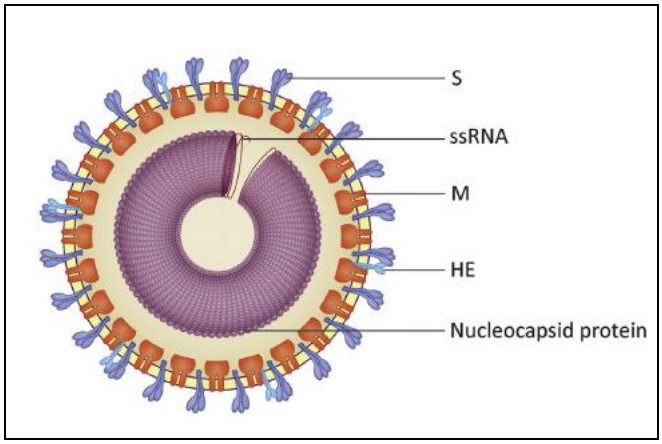


Figure 3: *Torovirus structure* **[6]**.

Members of the subfamily Coronavirinae are widespread among mammals, often causing only mild respiratory or enteric infections.

Over 60 coronaviruses (CoVs) have been isolated from bats (BtCoV) and most of these are in the genus beta-coronavirus. Bats serve as large (and highly mobile) CoV reservoirs; many bat species have their own unique BtCoV, suggesting a very long history of coevolution. Until 2002, CoVs were considered only minor pathogens of humans. However, an outbreak of severe acute respiratory syndrome (SARS) that began in 2002 was linked to infection with a new CoV (SARS-CoV).

The outbreak increased interest in CoV replication, distribution, evolution, transmission, and pathogenesis. In 2012, another coronavirus (distinct from SARS-CoV) was isolated in connection with an outbreak of severe respiratory disease in the Middle East. This virus, called Middle East respiratory syndrome coronavirus (MERS-CoV), continues to cause sporadic cases of severe respiratory illness.

Several important animal diseases are caused by CoVs. Infectious bronchitis virus (IBV) of chickens was the first CoV identified, in the 1930s. A pig coronavirus caused the deaths of millions of piglets in the United States in 2014. Feline CoV (FeCoV) may lead to FIP (Feline Infectious Peritonitis), a deadly disease of domestic cats. A rodent coronavirus, mouse hepatitis virus (MHV), has served for many years as a useful model system for investigating CoV replication and pathogenesis **[6]**.

1. Coronavirus genome organization

The 25-32 kb positive-strand RNA genome contains 7-10 open reading frames (ORFs). Almost two-thirds of the genome encodes nonstructural proteins (nsps) that are required for transcription and genome replication. Among these is nsp12, the large 930 amino acid RNA-dependent RNA polymerase (RdRp). Nsp12 forms a multiprotein complex with other CoV nsps. CoV nsps are synthesized as long precursor polypeptides, cleaved by virally encoded proteases (*Figure 4*).

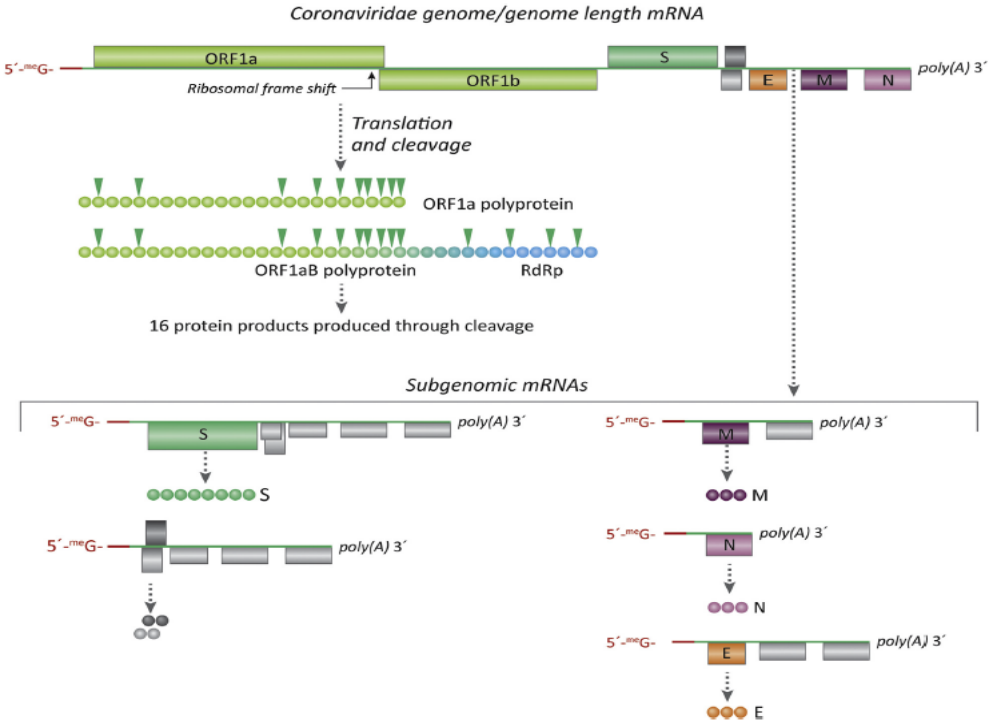


Figure 4: *Coronavirus genome organization and gene expression strategy* **[6]**.

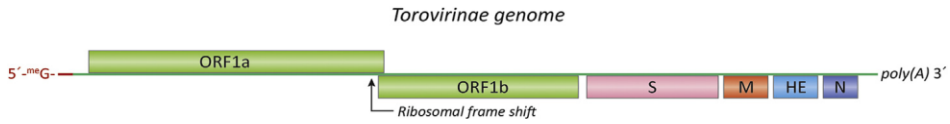


Figure 5: *Torovirus genome organization* **[6]**.

The *REP1a* polyprotein is cleaved to produce 11 smaller products (nsp1-nsp11; listed in Appendix *Table 2*). *Rep1b* follows *Rep1a* in the genome, separated from it by a frame-shifting site that is slightly upstream from the *Rep1a* stop codon.

About 20%-25% of the time, ribosomes reaching the frame-shift site will slip into the minus-1 reading frame and a longer polyprotein, called *REP1b* is synthesized. *REP1b* codes for five additional proteins, nsps 12-16, among which are the RdRp (nsp12), a protein with helicase and phosphatase activities (nsp13),

a protein with exonuclease and methyl transferase activities (nsp14), an endoclease (nsp15) and a second methyltransferase (nsp16). The guanine-N7-methyltransferase, nsp13, and the 2'O-methyl-transferase, nsp16, synthesize the CoV 5'-cap.

In addition to the final cleavage products, long-lived intermediates may have activities different from those of the fully cleaved products. 7 to 10 additional ORFs lie downstream of the replicase-associated genes. The largest of these encodes the spike (S) protein. The order (S, E, M, N) of the structural proteins on the coronavirus genome is well conserved. Dispersed among the structural protein genes are a variable number of additional small ORFs. These lie in-between, or overlap, the structural protein genes and they are not well conserved among CoVs. These are called accessory proteins (by convention they are named using the number of the shortest mRNA on which they are encoded). Mutation studies show that at least some of the accessory proteins are not required for coronavirus replication in cell cultures. However, mutating the accessory proteins does have a profound effect on the ability of the CoVs to replicate in their hosts and impacts viral pathogenesis.

As expected for an RNA virus, the CoV genome contains regulatory elements. Cis-acting regulatory elements are required for replication, transcription, and genome packaging. At the 5' end of the genome, elements that participate in viral RNA synthesis extend past the 5' untranslated region (UTR) and into the coding region of *rep1a*. This region folds up into a set of seven stem-loops.

Folding of the CoV 5’ RNA is dynamic, allowing for changing conformations that control critical aspects of RNA and protein synthesis. Functional analyses of cis-acting regulatory regions have shown that stability of RNA stem-loops can be critical for viral fitness.

At the 3’ end of the CoV genome, additional cis-acting elements are found in the 3’ UTR. The 3’ cis-acting elements are conserved (and are interchangeable) among beta-coronaviruses. As with the 5’ UTR, this region is probably dynamic, with different conformations controlling different steps in RNA replication/ synthesis.

Other important cis-acting sequences are those that direct ribosomal frame shifting near the end of the *rep1a* gene. Finally, genome packaging signals have been localized to internal regions of the H-CoV-SARS genome.

2. Virion structure

Coronavirus particles are enveloped with prominent spikes. Virions are spherical and range in size from 118 to 140 nm. Within the envelope is a flexible (subfamily Coronavirinae) or a doughnut-shaped (subfamily Torovirinae) nucleocapsid that consists of genomic RNA associated with the nucleoprotein (N). The spike (S) protein is the major glycoprotein that extends from the surface of the virion. Other membrane-associated proteins include membrane (M) and envelope (E).

3. Coronavirus structural proteins

All CoVs encode four structural proteins: Three membrane-associated proteins (S, M, and E) and a single nucleocapsid (N) protein. However, some beta-coronaviruses have an additional membrane protein with hemagglutinating and esterase activities, hence it is called HE. The order of the structural genes on the CoV genome is (HE) S, M, E, N (*Figure 4*). The order of structural genes on the torovirus genome is S, M, HE, and N (*Figure 5*).

- *The spike protein (S)* forms a prominent projection from the virus envelope and gives CoVs their characteristic appearance. S is glycosylated and is the attachment and fusion protein. Among the CoVs, there are some differences in the manner in which S is processed (cleaved into S1 and S2 fragments). S is always ER associated and modified by N-linked glycosylation. In many beta- and gamma-coronaviruses, S is partially or completely cleaved by host furin-like proteases in the ER (prior to assembly of new virions). The extent of proteolysis correlates with the number of highly basic residues at the S1/S2 cleavage site. The S1 (N-terminal) and S2 (C-terminal) products remain non-covalently associated.

  In contrast, HCoV-SARS S is not cleaved during assembly or release. Instead, it is cleaved in an acidified endosome during entry/penetration.

  It appears that there are two critical cleavage events that act in concert to mediate fusion: a cleavage at the S1/S2 boundary and a second cleavage within S2 (called the S20 cleavage site). Some CoV S proteins are not cleaved, but the terms S1 and S2 are still used to refer to the corresponding N- and C-terminal domains of the protein. It is also likely that, in some cases, processing of CoV S in cultured cells is not identical to the process in

the infected host. Comparisons of S1 sequences show that they diverge extensively and are not highly conserved, even within multiple isolates of a single type of coronavirus. We can reasonably speculate that sequence divergence is, at least in part, a result of host immune responses. In contrast to S1, the S2 product is highly conserved across the subfamily Coronavirinae.

- *The membrane protein (M)* is the most abundant protein in the virion. M contains three hydrophobic domains, thus is tightly associated with the virus envelope. M plays a major role in promoting membrane curvature. It has a short ectodomain (extracellular domain) that is modified by glycosylation. M also interacts with the N and E proteins. Expression of HCoV-SARS M (in the absence of other viral proteins) results in self-assembly and release of membrane enveloped vesicles. Virus-like particles are released when M is co-expressed with either N or E.
- *The envelope protein (E)* is found in very small amounts in the virion (about 20 molecules per virion), although larger amounts of E are present in infected cells. Different CoVs have variable requirements for E during particle formation, ranging from required for particle formation to not essential. In fact, virus titers close to 13106 pfu per mL have been reported for HCoV-SARS lacking the E protein. Studies show that E assembles in membranes to form ion channels, thus E is a viroporin. Viroporins influence the electrochemical balance in subcellular compartments.
- *The nucleocapsid protein (N)* is the only protein found in the ribonucleoprotein particle. N forms homodimers and homo-oligomers and binds genomic RNA, packaging it into a long flexible nucleocapsid. In the

infected cell, N localizes to the cytoplasm, and for some CoVs, N is also found in the nucleolus. N interacts with other CoV structural proteins, thus has a role in assembly and budding. N also colocalizes with replicase-transcriptase components and is required for RNA synthesis. Other roles for N include modulating cell-cycle (promoting cell-cycle arrest) and inhibiting host cell translation. An additional structural protein is found in most beta-coronaviruses, including the human coronavirus HCoV-HKU1.

- *The hemagglutinin-esterase (HE)* is a 48 kDa glycoprotein that projects outwards 5-10 nm from the virion. HE binds sialic acid units on glycoproteins and glycolipids. The esterase activity removes acetyl groups from O-acetylated sialic acid, thus may be a receptor-destroying enzyme.

4. Coronavirus replication cycle

The overall scheme of CoV replication is similar to that of other positive-strand RNA viruses, but the process for synthesis of sub genomic mRNAs is unique.

a) Attachment

CoV S is the receptor-binding protein. The receptors for some CoVs have been identified. Two human CoVs, HCoV-SARS, and HCoV-NL63 bind different regions of angiotensin converting enzyme 2 (ACE2). ACE2 is a cell-surface, zinc-binding carboxypeptidase important for regulation of cardiac function and blood pressure.

ACE2 is expressed in epithelial cells of the lung and small intestine, as well as many other organs. HCoV-MERS binds to dipeptidyl peptidase 4 (DPP4). Several other CoVs (FeCoV, FIPV, CCoV, and TGEV) bind to aminopeptidase N. However, not all CoVs bind to protein receptors. Bovine CV and the HCoV-OC43 bind to sialic acid units found on glycoproteins and glycolipids.

b) Penetration

CoVs are enveloped, so penetration occurs as a consequence of a membrane fusion event. Just as cleavage of the S protein varies among CoVs, so do the sites and requirements of the fusion process. CoV S proteins contain a hydrophobic "fusion peptide" that becomes exposed upon a large-scale rearrangement of S. The location and details of S rearrangement are variable, but can be triggered by factors such as proteolytic cleavage of S and/or acid pH.

HCoV-SARS S is found as an uncleaved product on extracellular virions. It is cleaved only after attachment and endocytosis. There are two critical cleavage events that precede (and are required for) fusion. One cleavage is at the S1/S2 boundary and the other is a cleavage within S2 (S20). Evidence supports cleavage at the S1/S2 boundary by cathepsin L; however, if one exposes HCoV-SARS to extracellular proteases (such as trypsin or elastase) in cell cultures, infection is greatly enhanced, suggesting that the endosomal proteases are not highly efficient. This may be relevant to HCoV-SARS-infection and pathogenesis: In the human respiratory tract, a transmembrane serine protease (TMPRSS2) is expressed in pneumocytes and binds to ACE2 (the receptor for HCoV-SARS).

The interaction between ACE2 and TMPRSS2 would conveniently put uncleaved S in close proximity to a host cell protease upon initial binding.

c) Amplification

The first synthetic event in the CoV replication cycle is translation of the viral genome by host cell ribosomes. *REP1a* and *REP1b* are translated from genomic RNA, and these polyproteins are necessary for virus replication to move forward. Some of the *REP1a* products (nsp3, nsp4, nsp6) have transmembrane

domains and these serve to anchor the replication-transcription complex to cell membranes, a prerequisite for synthesis of additional viral RNAs. The interaction also causes remodeling of host cell membranes to form structures dedicated to virus RNA synthesis.

d) RNA Synthesis

In vitro, the CoV RdRp requires a primer, specifically a short RNA oligonucleotide. It so happens that the CoVs encode two different proteins with RdRp activity. The nsp8 gene product is thought to be a primase capable of synthesizing short oligonucleotides.

Nsp12 is the elongating polymerase. Other viral nsps in the replication-transcription complex are involved in cap synthesis (*Appendix Table 2*). CoVs also encode two ribonucleases. NendoU (nsp15) is a Nidovirales endonuclease that cleaves both single and double-stranded RNA, cutting downstream of uridylate residues. ExoN (nsp14) is a 3'-5' exonuclease. CoVs with mutations in ExoN have an enhanced mutation rate suggesting a role for ExoN in proofreading during RNA synthesis.

In addition to genome-length RNA, a set of sub-genomic (sg) mRNAs is found in the infected cell. The sg mRNAs are used for the expression of the structural and accessory proteins. All are capped and polyadenylated and they share a common 3' end forming a so-called "nested set" of mRNAs. A closer look at the sg mRNAs reveals that each contains an identical leader sequence of 70-100 nt at the 5' end. The leader sequences found on all sg mRNAs are identical; however, this sequence is found only once in the genome, near the 5' end. Leader sequences are fused to downstream sequences (sometimes called the body RNAs) at short, 8-9nt motifs called the transcription regulating sequence

(TRS). A TRS is found upstream of the ORFs-encoding structural proteins (which are called TRS body or TRS-B). A TRS is also present just downstream of the leader sequence in the 5' UTR. These findings provide clues to the unique strategy used for CoV mRNA synthesis: CoV sg mRNAs are generated by a process of discontinuous transcription (*Figure 6*).

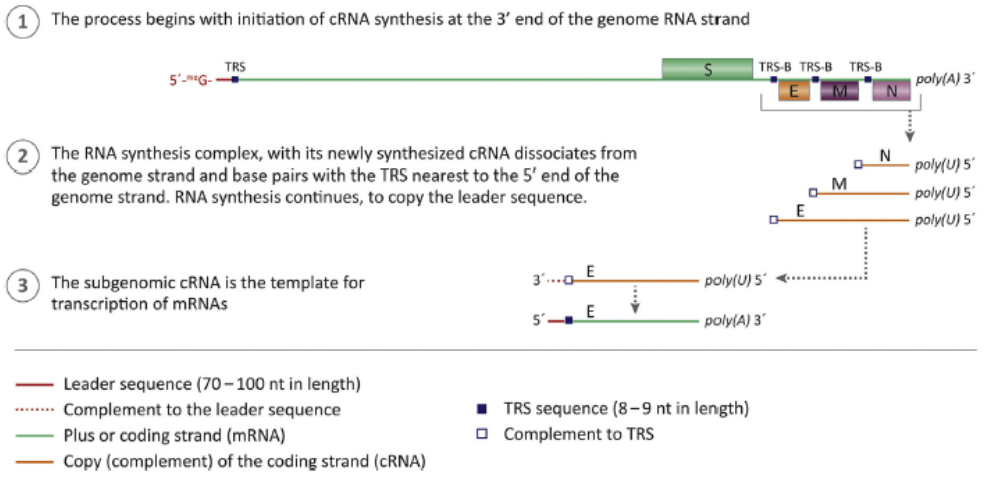


Figure 6: *Coronavirus discontinuous transcription* **[6]**.

Discontinuous transcription very likely contributes to the high level of CoV genome recombination. This type of RNA virus genome recombination is called a copy-choice mechanism (*Figure 7*). Quantification of CoV RNAs presents in infected cells shows that cRNAs (negative-sense RNAs with 50 oligo (U)) are present at levels 0.1-0.01 times lower than "positive-sense" genomes and mRNAs. This finding suggests that recombinants are more likely to occur during synthesis of negative strands.

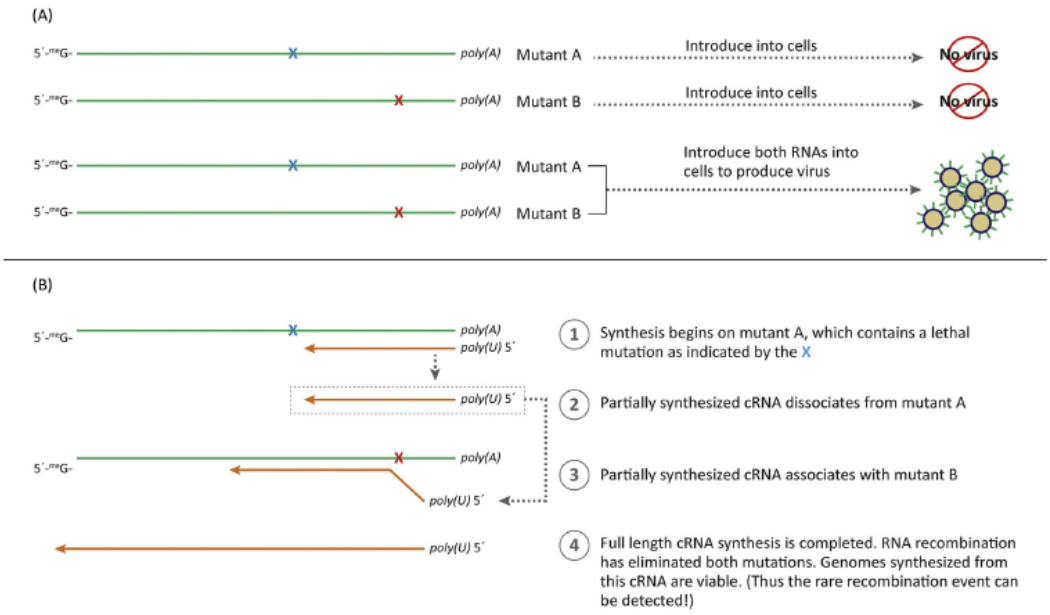


Figure 7: *Coronavirus RNA recombination* **[6]**.
(A): If individual mutant coronaviruses are used to infect cells there is no virus growth. However, if mutants are used together to infect cells, virus growth is restored suggesting that genome recombination has occurred.
(B): This Panel illustrated the mechanism of RNA copy choice 'recombination'.

e) Assembly and Release

Virion assembly takes place on membranes. Genomic RNA is bound by N protein, associates with M protein and buds into ER/Golgi membranes. M packs tightly into membranes and is thought to cause the membrane curvature that drives budding. S and E are also membrane proteins and are acquired during the budding process. The ion channel activity of E is that of a viroporin; it alters cell secretory pathways to promote virus release. A function of E may be to increase the pH of the transport vesicles. Virus particles contained within membrane bound vesicles are released from cells by exocytosis.

5. Diseases caused by coronaviruses

Most animal and human CoVs are transmitted by the fecal-oral route and their initial replication site is in epithelial cells where virus production causes local respiratory symptoms or diarrhea. However, on occasion, CoVs cause severe to fatal disease.

a) Severe Acute Respiratory Syndrome

SARS facts:

- SARS-CoV emerged in the human population in China in 2002.
- Epidemiologic studies- and genetic analysis indicated the virus most likely jumped from bats into farm raised Himalayan palm civets (Paguma larvata) and then into humans.
- Human to human transmission was by respiratory and fecal routes.
- Approximately 8000 cases were reported worldwide.
- Twenty-six countries were affected.

- Seven hundred and seventy-four deaths occurred (B10% case mortality rate).
- Economic losses in Hong Kong were 5.9 billion (USD).
- In July 2003, WHO reported that the last known human chain of transmission was broken.
- Bats and birds are natural reservoirs of SARS-like viruses.
- Laboratory-associated infections occurred in China in 2004.

SARS-infection causes a triphasic pattern of disease. The first phase is nonspecific with fever, cough, sore throat, and myalgia. Breathing difficulties (dyspnea) show up 7 to 14 days after appearance of the first symptoms. The second phase of the disease includes shortness of breath, fever, onset of hypoxia, and often diarrhea. In the most serious cases, patients progress to a third phase with development of acute respiratory distress requiring hospitalization and mechanical respiration.

b) Middle East Respiratory Syndrome

MERS facts:

- MERS begins with coughing, fever, and breathing problems but may progress to pneumonia and kidney failure.
- Over 1600 human cases and the outbreak is ongoing.
- Case fatality rate was 30%.

- Cases are sporadic and cannot be linked to a single source (based on genome sequencing).
- Countries most affected include those in the Arabian Peninsula (Bahrain, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, United Arab Emirates, and Yemen).
- Casual transmission from person to person very rare.
- Most person to person transmissions occurs in a hospital setting.
- Many healthy camels in the Arabian Peninsula have antibodies specific to CoV-MERS (indicating past infection) but infections often occur among people with no known contact with camels.
- A virus very similar to CoV-MERS has been found in some bats (sequence analysis suggests that the virus moved from bats to camels).
- Many questions about the epidemiology of CoV-MERS remain unanswered.

Sporadic cases of MERS continue to be reported. Strict infection control procedures in hospitalized patients limit person to person spread in that setting and transmission among casual or household contacts is rare.

While MERS-CoV and SARS-CoV are both beta-coronaviruses, they derive from different sources and have unique characteristics. SARS-CoV has a tropism for ciliated respiratory epithelial cells and its receptor is ACE2. In contrast MERS-CoV has a tropism for non-ciliated respiratory epithelial cells and its receptor is DPP4. The propensity for CoV recombination, and their ubiquitous presence in bats, makes a case for close surveillance and study of these potential human pathogens.

c) *Feline Coronavirus and Feline Infectious Peritonitis*

FeCoV is the most common virus found in cat fecal samples and is spread through the fecal-oral route. Infection is usually subclinical or associated with a transient, mild diarrhea. Immunity to FeCoV is neither solid nor long-lasting. As antibody levels decrease, cats may be reinfected and once again experience mild diarrhea. Most kittens infected with FeCoV clear the virus, but about 15% become chronic shedders. Chronic shedders are at highest risk for developing FIP, a systemic (multiorgan), lethal disease. FIP develops when enteric FeCoV mutates to become capable of infecting monocytes and macrophages. This results in systemic viral infection, as the virus is no longer confined to the digestive tract. The virus associated with monocytes/macrophages is called the FIP biotype. Mutation occurs independently within each cat, with every FIP biotype virus having unique genetic features.

Specific viral genes (for example, the orf3C protein) are important for the change in cell tropism. After that, the virus continues to mutate, becoming better adapted to peritoneal macrophages. This occurs despite preexisting host immune responses. Early signs of FIP are nonspecific and include anorexia, weight loss, inactivity, and dehydration. FIP can occur in any age cat, but cats less than 1 year of age or greater than 10 years of age are more susceptible. Constant virus replication in macrophages leads to B-cell activation and production of nonprotective (non-neutralizing) antibodies. In fact, immune complexes are damaging as they activate the complement system and lead to immune-mediated vasculitis. The classic lesions associated with the severest form of FIP are aggregates of macrophages, neutrophils, and lymphocytes that form in very small veins. These aggregates are called pyogranulomas and they are associated with development of edema and accumulation of large volumes of protein-rich fluids **[6]**.

6. The Host defense against SARS-CoV-2

In the early stages of infection, SARS-CoV-2 triggers cells **[11]**, like nasal and bronchial epithelial cells and pneumocytes, using the viral structural spike (S) protein that will bind to the angiotensin-converting enzyme 2 (ACE2) receptor (*Figure 8*) **[12]**. Transmembrane serine protease type 2 (TMPRSS2), by cleaving ACE2 and activating the S protein of SARS-CoV-2, facilitates viral uptake and allows coronaviruses to enter host cells. **[12]**. ACE2 and TMPRSS2 are both expressed in host target cells, especially alveolar epithelial type II cells **[13][14]**. Severe lymphopenia may occur in individuals with COVID-19 since SARS-CoV-2 infects and kills T lymphocyte cells, similarly to other respiratory viral diseases, such as influenza. Although ACE2 receptor upregulation by ACE inhibitors and angiotensin receptor blockers has been suggested to increase the risk of SARS-CoV-2 infection, large observational cohorts have not identified a significant link between these drugs and the possibility of infection or hospital mortality induced by COVID-19 **[15][16]**. For example, in a Danish study including 4480 patients infected by SARS-CoV-2, previous treatment with ACE inhibitors or angiotensin receptor blockers was not linked to mortality **[16]**.

In later stages of infection, the integrity of the epithelial-endothelial barrier is breached. SARS-CoV-2 infects endothelial cells in pulmonary capillaries, as well as epithelial cells, which leads to and intensification of the inflammatory response and an influx of monocytes and neutrophils.

Interstitial mononuclear inflammatory infiltrates and edema develop and appear as ground-glass opacities on CT scan. This results in pulmonary edema filling the alveolar spaces with formation of a hyaline membrane, consistent with the early phase of acute respiratory distress syndrome (ARDS) **[17]**. Bradykinin-dependent lung angioedema may also contribute to disease **[18]**. Taken together, disruption of the endothelial barrier, dysfunction of alveolar-capillary oxygen transmission, and compromised oxygen diffusion capacity are characteristic elements of COVID-19.

In severe cases of COVID-19, a fulminant activation of clotting cascade and consumption of coagulation factors take place **[19][20]**. A Chinese report found that 71% of 183 COVID-19 deaths met criteria for diffuse intravascular coagulation **[19]**. Inflamed lung tissues and pulmonary endothelial cells may lead to the formation of microthrombi and so to the high occurrence of thrombotic complications, like deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (e.g., limb ischemia, ischemic stroke, myocardial infarction) in patients that are critically ill **[21]**. The development of viral sepsis, identified as life-threatening organ dysfunction due to a dysregulated host response to infection, may further lead to multiorgan failure.

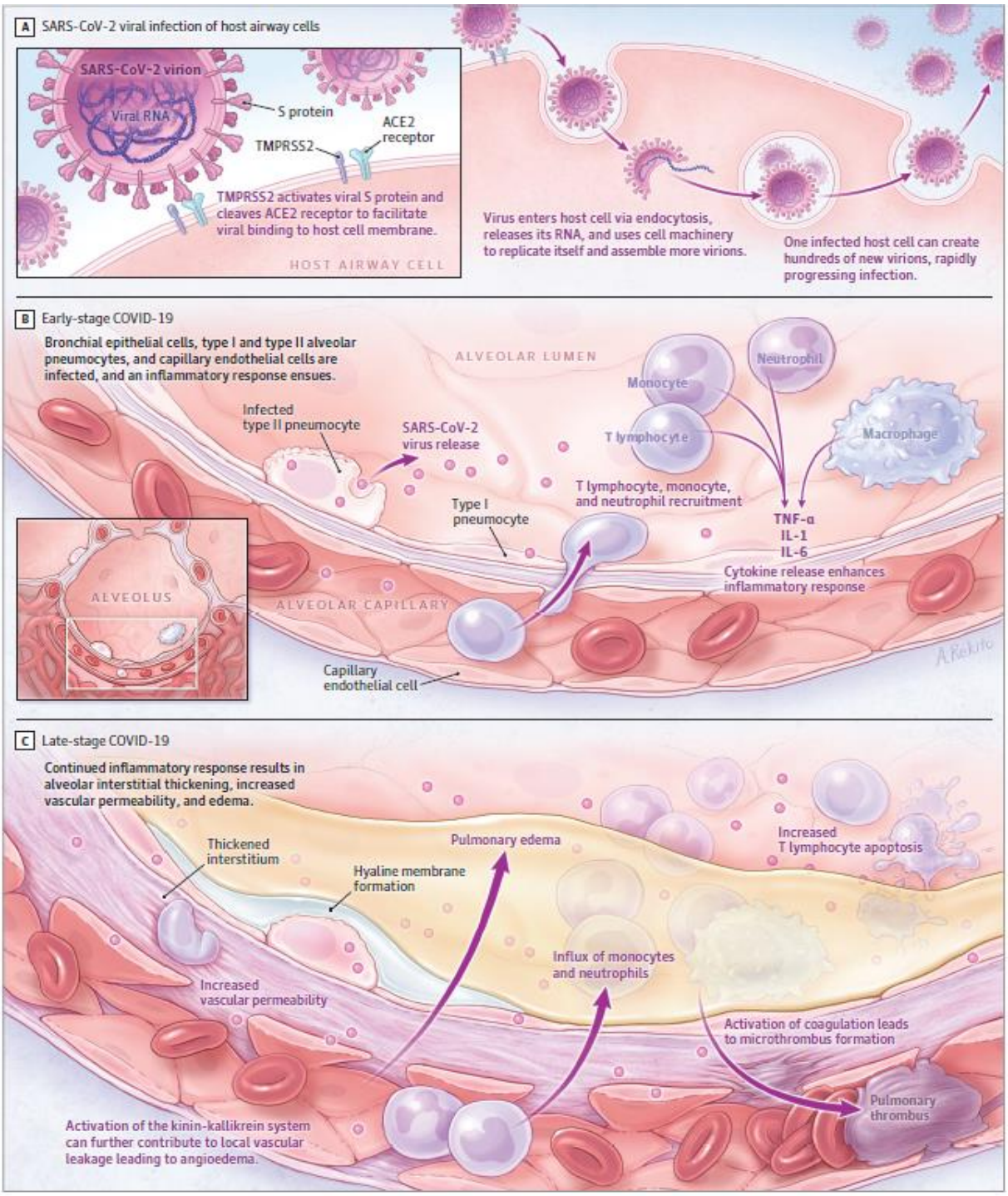


Figure 8: *Immunopathogenesis of Coronavirus Disease 2019 (COVID-19)* **[11]**.

B. Host

Coronaviruses are respiratory pathogens of relatively high virulence, from a virus family that has an unusual knack of jumping species boundaries **[22]**.

Early genomic comparisons revealed that the most closely related viruses to SARS-CoV-2 came from bats **[23]**. Sampling in recent years has identified an impressive array of bat coronaviruses, including RaTG13 and RmYN02 **[24]**. Hence, bats are undoubtedly important reservoir species for a diverse range of coronaviruses **[25]**. Despite this, their exact role in the zoonotic origin of SARS-CoV-2 is not established **[26]**.

Although bats are likely the reservoir hosts for this virus, their general ecological separation from humans makes it probable that other mammalian species act as ‘‘intermediate’’ or ‘‘amplifying’’ hosts, within which SARS-CoV-2 was able to acquire some or all of the mutations needed for efficient human transmission.

In the case of SARS and MERS, civets and camels, respectively, played the role of intermediate hosts, although as MERS-CoV was likely present in camels for some decades before it emerged in humans during multiple cross-species events, these animals may be better thought of as true reservoir hosts **[27]**.

This is highlighted by the recent discovery of viruses closely related to SARS-CoV-2 in Malayan pangolins (Manis javanica) illegally imported into southern China. The pangolin viruses are particularly closely related to SARS-CoV-2, containing all six of the six key mutations thought to shape binding to the ACE2 receptor, and exhibiting 97% amino acid sequence similarity.

The fact that they carry a virus related to SARS-CoV-2 strongly suggests that a far greater diversity of related beta-coronaviruses exists in a variety of mammalian species but has yet to be sampled **[22]**.

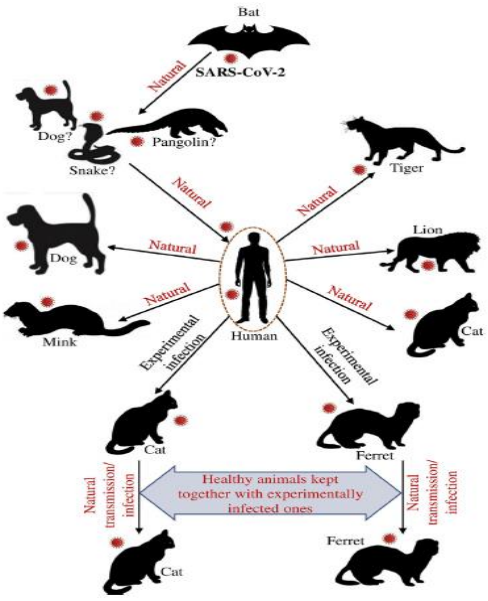


Figure 9: *Host range of SARS-CoV-2. Different pets/animals are susceptible to SARS-CoV-2 might be occurred naturally and/or experimentally* **[28]**.

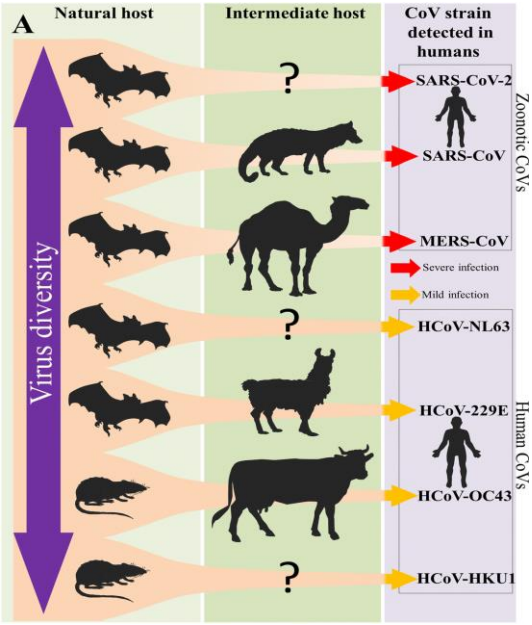


Figure 10: *Summary of the groups of animals that serve as natural and intermediate hosts for the seven CoVs that can cause disease in humans* **[10]**.

C. Transmission methods

To date, conclusive evidence exists for respiratory transmission of SARS-CoV-2 and transmission to and between certain domestic and farm animals, as well as rare vertical transmission. Direct contact or fomite transmission is suspected and may occur in some cases. Sexual, fecal-oral, and bloodborne transmission are theorized but have not been documented **[29]**.

1. Respiratory transmission

When a virus spreads through respiratory transmission, it does so either with virions suspended on large droplets or fine aerosols expelled from the respiratory tract of the primary case patient. Droplets are typically considered to be particles larger than 5 micro-meter that fall to the ground within about 6 feet and aerosols to be particles smaller than 5 micro-meter that can remain suspended in the air for prolonged periods; however, this dichotomization may be an oversimplification, and distinguishing droplet and aerosol transmission is difficult in clinical settings **[30-32]**.

The dominant route of transmission of SARS-CoV-2 is respiratory **[33]**. Growing evidence indicates that infectious virus can be found in aerosols and in exhaled breath samples **[34-36]**, and it is likely that under certain circumstances, including during aerosol-generating procedures, while singing, or in indoor environments with poor ventilation, the virus may be transmitted at a distance through aerosols.

Nevertheless, there is abundant evidence that proximity is a key determinant of transmission risk **[37][38]**. A detailed contact tracing study of train passengers that included 2334 index cases and 72093 close contacts found that the secondary attack rate was closely linked to both the distance between seats and the duration of shared travel **[39]**.

That proximity so clearly increases risk for infection suggests that classic droplet transmission is more important than aerosol transmission **[38]**.

The role of ventilation in preventing or promoting spread also highlights the importance of respiratory transmission.

Poor ventilation has been implicated in numerous transmission clusters, including those in bars, churches, and other locations **[40-42]**. By contrast, such events have rarely occurred outside, and then only in the context of crowding **[43-45]**.

In addition, studies have found that masking, both in health care settings and in the community, decreases transmission of SARS-CoV-2 **[38]**. All of this evidence supports the dominant role of respiratory spread of this virus.

2. Direct contact and fomites

There is currently no conclusive evidence for fomite or direct contact transmission of SARS-CoV-2 in humans.

Reports suggesting fomite transmission are circumstantial. For example, in a cluster of infections associated with a mall in China, several affected persons reported no direct contact with other case patients **[46]**.

The investigators noted that these individuals used shared common facilities (such as elevators and restrooms) and proposed fomite or respiratory transmission in those settings. As noted in the description of all known transmission clusters in Japan, it can be difficult to identify primary cases in large health care–associated outbreaks **[42]**. Poor hand hygiene was associated with increased risk for infection among health care workers, and daily use of chlorine or ethanol cleaning products in the household was associated with decreased risk **[47][48]**. Although this might indirectly suggest direct contact or fomite spread, it can be difficult to tease out the relative importance of simultaneous interventions because, for example, excellent hand hygiene may be associated with better infection control practices overall. Live virus can be isolated after the period of infectiousness, which suggests a minimum necessary

inoculum to initiate infection **[49][50]**. On the basis of currently available data, we suspect that the levels of viral RNA or live virus transiently remaining on surfaces are unlikely to cause infection, especially outside of settings with known active cases.

3. Domestic pets and farm animals

Several studies have documented that SARS-CoV-2 can infect domestic animals, including cats, dogs, and ferrets **[51-54]**. The virus replicates well in cats (but not in dogs) and is transmissible between cats and ferrets **[53][55]**. There are no confirmed cases of transmission from domestic pets to humans. Minks are susceptible to SARS-CoV-2 infection and are farmed in some areas where cases of transmission from minks to human farm workers is suspected **[56][57]**.

4. Vertical transmission

Many studies have evaluated the possibility of vertical transmission of SARS-CoV-2 **[58]**. There are several reports of positive SARS-CoV-2 IgM in neonates **[59][60]**. Although IgM does not cross the placenta, and thus its presence may indicate in utero infection, IgM testing is prone to false positivity, particularly in the setting of significant inflammation **[61]**. There are also several reports of early nasopharyngeal positivity on polymerase chain reaction testing after delivery in neonates, including a description of 3 infants with positive results on day 2 of life and another of an infant with positive results 16 hours after delivery **[62][63]**. Several case reports have found placental infection by SARS-CoV-2, and one has shown transplacental transmission **[64-67]**. In addition, breast milk can harbor viral RNA, although no confirmed transmissions to infants from breast milk have been reported **[68-70]**. Taken together, these studies suggest that vertical transmission of SARS-CoV-2 rarely occurs.

5. Fecal–Oral (or fecal aerosol) transmission

Fecal– oral transmission was theorized early in the outbreak because of the known high concentration of ACE2 receptors in the small bowel **[71]**. No evidence currently supports fecal– oral transmission in humans, and intragastric inoculation of SARS-CoV-2 in macaques did not result in infection **[72]**. Although viral RNA is commonly detected in stool, live virus has only rarely been isolated **[73-77]**. This has led some to wonder whether viral aerosolization with toilet flushing could lead to transmission **[78]**. In February 2020, there were news reports of an outbreak from possible fecal aerosol transmission at a multistory apartment complex in Hong Kong; however, an investigation showed that the secondary case patients were likely infected during a dinner party **[79]**. One study did find low detectable levels of RNA in air samples near patient toilets at a hospital in Wuhan, although isolation of live virus was not assessed **[80]**. The spatial distribution of a cluster of 3 infected families living in vertically aligned apartments connected by drainage pipes in a high-rise apartment building in Guangzhou, China, as well as the presence of viral RNA in another vertically aligned, unoccupied apartment, suggests the possibility of fecal aerosol transmission in rare cases **[81]**. Taken together, given how rarely live virus has been isolated from stool, the low levels of replication-competent virus in stool that might be aerosolized from toilet flushing seem highly unlikely to cause infection except under unusual or extraordinary circumstances.

6. Sexual transmission

No current evidence supports sexual transmission of SARS-CoV-2. Viral RNA has been found in semen, although infectious virus has not been isolated **[82]**. Vaginal fluid has been negative except in a single case that reported RNA with a low viral level **[83][84]**. For linked transmissions between sexual partners, exclusion of respiratory transmission would not be possible.

7. Bloodborne transmission

The proportion of persons with viral RNA detectable in blood is currently unknown. An early study found viral RNA in only 3 of 307 blood specimens **[73]**.

Another study detected viral RNA in 32.9% of 85 blood samples from symptomatic persons, including 22 of 28 from those requiring hospitalization **[85]**. In another study, viral RNA was detected in 27% (19 of 71) of hospitalized patients and 13% (2 of 16) of outpatients with COVID-19 **[86]**. Viral RNA was found in blood from 4 blood donors without symptoms. The samples were discarded and not administered to other patients **[87]**. To date, no replication-competent virus has been isolated from blood samples, and there are no documented cases of bloodborne transmission.

8. Viral and host factors affecting transmission

The Binding of the viral spike (S) protein to the host ACE2 receptor is a critical step for cell entry, and as a result, host ACE2 distribution determines viral tropism **[88][89]**. Viral load is highest in the upper respiratory tract (nasopharynx and oropharynx) early in disease and then increases in the lower respiratory tract (sputum), suggesting that the upper respiratory tract is the usual initial site of viral replication, with subsequent descending infection **[90]**. Susceptibility to SARS-CoV-2 infection increases with age; children younger than 10 years are around half as susceptible as adults **[91-94]**. Viral RNA testing of household contacts in Iceland showed 6.7% and 13.7% positivity in children and adults, respectively, and testing in Wuhan, China, showed 4% and 17.1% positivity **[95][96]**. Decreased ACE2 expression in children compared with adults may partly explain the lower susceptibility seen in children **[97][98]**.

The relative probability of transmission from an infected child compared with

that from an adult is not well understood. Replication-competent virus is readily isolated from children who are infected, and there are conflicting reports about the relative viral loads in children compared with adults, with some studies not controlling for time since symptom onset, a key determinant of viral load **[98-101]**. Multiple large contact tracing studies have suggested a lower secondary attack rate for young children, but these must be interpreted with caution because children are less likely to have symptomatic disease and therefore less likely to be identified as index cases **[101-104]**. Moreover, these studies predominantly took place during periods of school closures, which may have had a confounding effect on the likelihood of a child being an index case.

One study of households in the United States found that household contacts of patients with immune-compromising conditions and COVID-19 had increased risk for infection, a finding that has not yet been replicated but which suggests that this population may be more likely to transmit the virus **[105]**.

Viral factors may also contribute to transmissibility. For instance, a marked increase in the prevalence of SARS-CoV-2 bearing a D614G mutation has been noted over time **[106]**. Whether this mutation provides a selective advantage to the virus has been debated **[107]**. It has now been shown that this variant infects human ACE2 cell lines more efficiently than wild-type virus, that progeny virus has increased expression of S protein, that the S protein has a higher rate of binding to ACE2, and that in vivo, viral loads may be higher for this variant **[106-110]**.

D. Epidemiological aspects

1. Geographic distribution

- ***In the world***

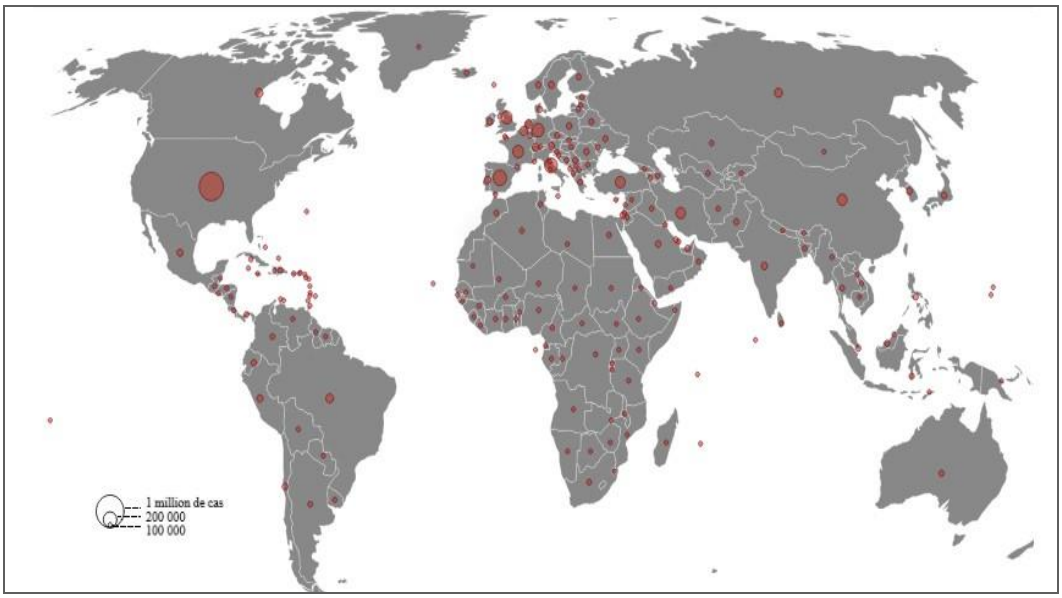


Figure 11: *Distribution of the number of confirmed cases of COVID-19, in all the countries, as of April 20, 2020* **[111]**.

- ***In Morocco***

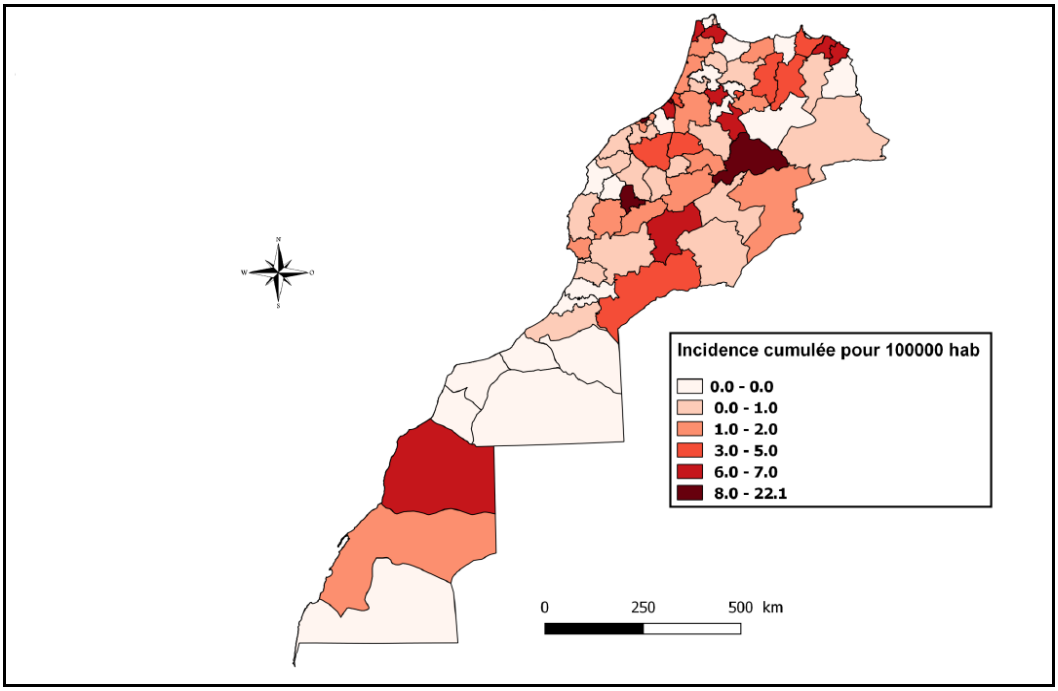


Figure 12: *Mapping the cumulative incidence of COVID-19 per 100.000 inhabitants in the provinces and prefectures of Morocco. April 17, 2020* **[112]**.

2. Case count

a) Case progression

- ***In the world***

As of December 11, 2021, we report a total number of 270.144.331 confirmed cases. There are currently 21.909.849 active cases, of which 88.779 are critical (0.4%) **[5]**.

- ***In Morocco***

By the end of 2021, 951.380 cases have been reported. Presently, there are 1.845 active cases, among which 347 are critical (18.8%) **[5]**.

b) Outcome of cases

- ***In the world***

There has been a total of 242.913.953 recovered cases (98%) and only 5.320.529 deaths (2%) **[5]**.

- ***In Morocco***

There has been a total of 934.739 recovered cases (98.4%), and only 14.796 deaths (1.6%) **[5]**.

E. Prevention

On 23 January 2020, the Chinese government introduced control measures designed to limit spread of the disease, including travel bans, along with social distancing policies, isolation of cases and quarantine of suspected contacts **[113]**.

In Morocco, the first case of COVID-19 was reported on March 2nd, 2020. Ever since, drastic measures have been taken in order to contain and limit the spread of the virus within the kingdom.

- March 15, 2020: Closure of land, air and sea borders.
- March 16, 2020: Cessation of schooling for all school and university levels, progressive confinement of the population, which remains nevertheless partial.
- March 20, 2020: State of alert (Decree) total confinement (exception supply) **[112]**.

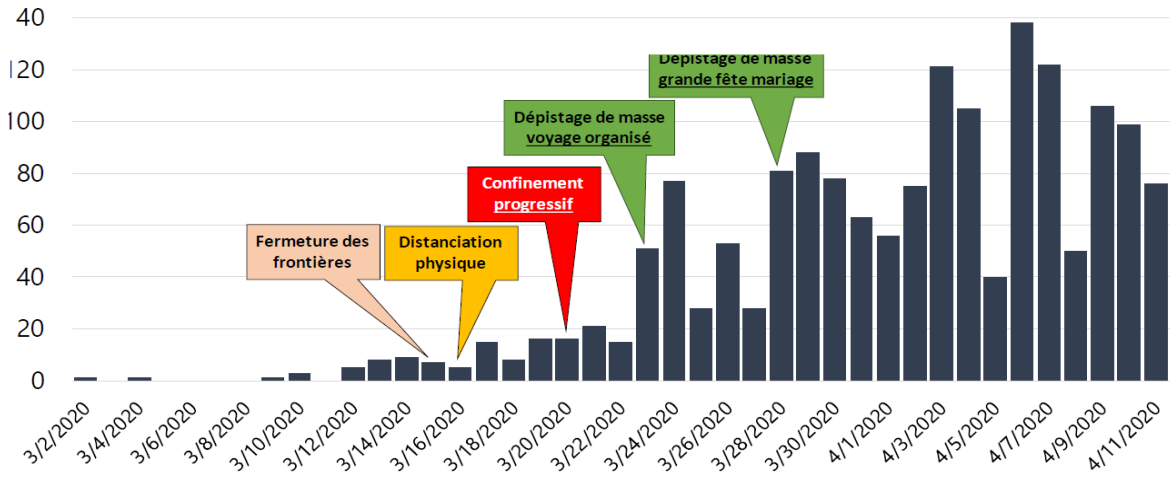


Figure 13: *Newly affirmed cases of COVID-19 in Morocco, by date of management* **[112]**.

In addition, other measures have been taken on an individual level, such as the mandatory wearing of masks, hand sanitizing, social distancing, the limitation of the number of individuals in closed spaces even after the lifting of the generalized confinement.

For the medical and nursing staff, specific protective measures have been put in place to protect them in the performance of their duties, namely the provision of training and awareness sessions on the risks of the disease as well as the way of wearing of personal protective equipment (PPE), the exclusion of pregnant women and staff with chronic illnesses or immune deficiencies, as well as the administration of post-exposure chemoprophylaxis to health care staff who have provided care without protective measures to a confirmed COVID-19 patients (Appendix *Figure 1*) **[112]**.

III. DIAGNOSIS

A. Clinical

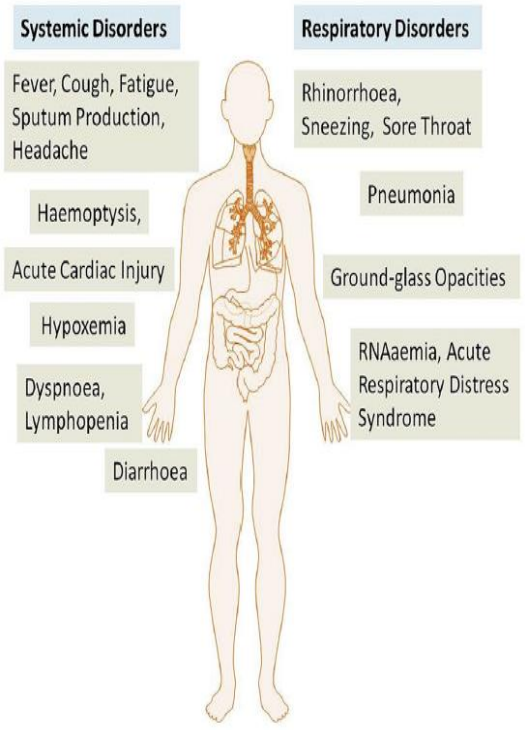
The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days **[114][115]**. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days **[116]**. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients > 70 years old compared with those under the age of 70 **[116]**. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia **[117][118][116] [119]**.

Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of ground-glass opacities that led to death **[118]**. In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs **[120]** that likely induced both systemic and localized immune response that led to increased inflammation.

It is important to note that there are similarities in the symptoms between COVID-19 and earlier beta-coronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans **[118]**. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhea, sneezing, and sore throat **[121][122]**. In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnea with hypoxemia **[123]**.

Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar gastrointestinal distress. Therefore, it is important to test fecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc. **[121][122]** (*Figure 14*).

Hence, development of methods to identify the various modes of transmission such as fecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease.



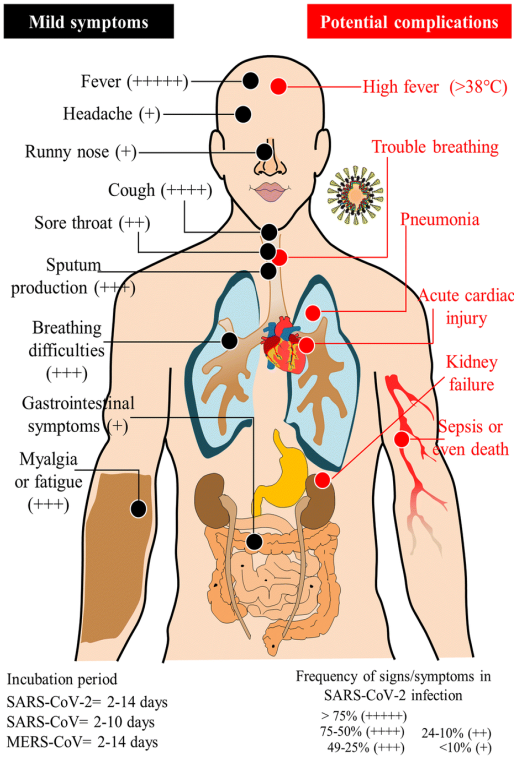


Figure 15: *The systemic and respiratory disorders caused by COVID-19 infection* **[114]**.

Figure 14: *Common signs and symptoms after infection with CoV: SARS, MERS and novel SARS-2 Coronaviruses* **[10]**.

B. Para clinical

1. RT-PCR

Reverse transcription polymerase chain reaction (RT-PCR) is a laboratory technique combining reverse transcription of RNA into DNA, and amplification of specific DNA targets using polymerase chain reaction (PCR). It is primarily used to measure the amount of a specific RNA. This is achieved by monitoring the amplification reaction using fluorescence, a technique called real-time PCR or quantitative PCR (qPCR). Combined RT-PCR and qPCR are routinely used for analysis of gene expression and quantification of viral RNA in research and clinical settings **[124]**.

Real-time reverse transcription polymerase chain reaction (RT-qPCR) is widely used to detect gene expression levels **[125]**, while also facilitating the rapid diagnosis of acute respiratory viral infections **[126]**. COVID-19 can be diagnosed in the laboratory by detecting SARS-CoV-2 genes in clinical samples collected from suspected patients, followed by viral isolation and culture **[127]**. RT-qPCR is commonly used worldwide to diagnose COVID-19 in the laboratory setting **[126][128][129]**.

An RT-qPCR-based assay for detecting SARS-CoV-2 was first developed at the Charité Institute of Virology in Germany, and introduced by the WHO on January 13, 2020 **[126]**. The assay targets the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) gene, as well as the E and N genes **[130]**.

2. Antigenic test

As an alternative to nucleic acid amplification tests (NAATs), numerous point-of-care antigen test (AgPOCT) for direct virus detection are currently available **[131]**. As opposed to NAATs, these tests detect viral protein antigens by immunological means in naso- or oropharyngeal swabs. Similar to NAATs, test performance is hugely influenced by preanalytical factors like the quality of the swab itself or the sample extraction. These tests, however, are easy to perform, do in theory not require highly trained staff or specialized laboratory equipment, and yield results in only a couple of minutes (generally, around 15min).

The virus detection limit (LOD = Limit of Detection: copies / ml or TCID50/ml) of rapid antigen tests is significantly higher (by several powers of ten) compared to molecular genetic testing methods (e.g., NAAT) **[132]**. Reliable statements on the effects of the increased LOD of antigen tests on diagnostic sensitivity and specificity or predictive value in clinical practice are lacking, especially in a real-life context at the point-of-care, where the tests are performed by patient's caretakers rather than by highly trained and specialized laboratory staff **[132][133]**.

3. Imaging

a) Chest X ray

Chest radiography is a medical imaging technique using X-rays to diagnose pathologies affecting or impacting the thorax and its components: mediastinal damage, pulmonary infections, pneumothorax, cardiac decompensation, etc...

- ***Rooms and projections***

Chest radiography is usually the primary imaging test performed in patients with suspected or confirmed COVID-19, even if it is less sensitive than computed tomography (CT), because of its accessibility, and low cost **[134][135]**. The ideal chest radiograph consists of a posteroanterior (PA) and lateral projections with the patient in a standing position. It is the only radiography test that can be performed in critically ill and ICU patients. Its interpretation is frequently limited by the low degree of inspiration and by the enlargement of the cardio-mediastinal silhouette due to the AP projection. However, it can detect possible complications, and allows serial monitoring of the course of the disease **[134][136]**.

- ***Sensitivity***

One of the restrictions of chest radiography, is the high incidence of false negatives. It may be a result of:

- Early realization of the imaging test and the absence of pulmonary disease at presentation,
- The fact that the typical findings of COVID-19, namely ground-glass opacities and reticular pattern, can be hard to detect.

On the other hand, false positives may be caused by:

- Lack of inspiration,
- Breast prominence,
- Poor positioning of patient, which induces increased density of the lung periphery and mimics the appearance of ground glass opacities.

Although there are differences between PCR, CT and portable X-ray regarding sensitivity, it is admitted that the latter can be used as a triage mean in certain situations **[135][137][138][139]**:

- Areas where there is a high incidence of SARS-CoV-2 infection,
- Centers with limited access to PCR, CT and rapid tests, but with availability of portable chest X-ray systems,
- Critically ill patients, so as to accelerate their classification, hospital admission and treatment.

b) CT scan

Computed tomography is a medical imaging technique that consists of measuring the absorption of X-rays by tissues and then, by computer processing, digitizing and finally reconstructing 2D or 3D images of anatomical structures. To acquire the data, the tomographic or "slice" analysis technique is used, by subjecting the patient to the scanning of an X-ray beam.

- ***Controversy: CT scan as a screening tool?***

Some studies have shown that computed tomography positive results might be prior to positive RT-PCR results. In fact, CT scan sensitivity can be up to 97% **[140][141]**. However, because of its low specificity (25%), and the fact that COVID-19 findings are similar to those in other viral pulmonary infections, there are debates concerning the use of CT as a diagnosis modality, and most associations, such as the ACR, consider it as a second-line technique **[142]**. Other associations with PCR testing limitations, such as the Chinese association, justify the use of CT as the initial diagnosis modality by its higher sensitivity, and its lower likelihood of false negatives, especially in the early stages of the

disease **[136][140][143]**.

- ***Technique***

Most authors recommend to perform a chest study in inspiration without intravenous contrast for the initial evaluation of COVID-19 with CT **[144-146]**. It is also advisable to use faster rotation times (≤ 0.5 sec) and higher pitch values (> 1:1) to prevent motion artefacts, since many patients present with dyspnea or cough **[146]**. Patients with COVID-19 may require multiple imaging testing in short notice, leading to an increase in cumulative radiation that must be taken into account, especially in the most sensitive populations **[147][148]**.

IV. EVOLUTION OF THE PANDEMIC

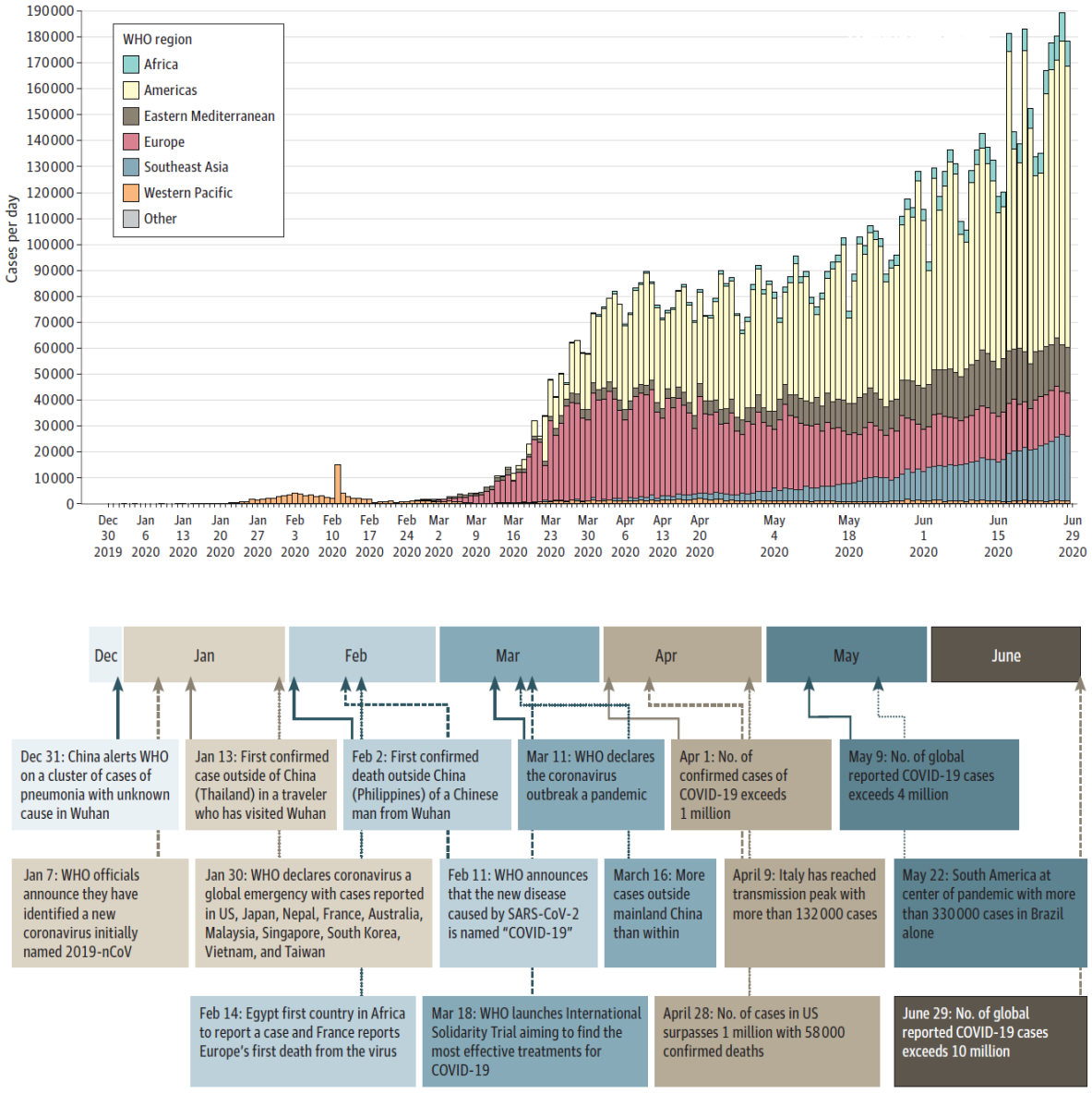


Figure 16: *Key events in the early Coronavirus Disease 2019 (COVID-19) pandemic* **[11].**

Materials And Methods

I. TYPE AND POPULATION OF STUDY:

It is a retrospective descriptive and analytical study, including patients suffering from COVID-19, confirmed with a positive testing by RT-PCR, admitted to the Center for Virology and Infectious and Tropical Diseases (CV MIT), From March 16 to June 16, 2020.

II. DATA INTAKE FORM:

The Data intake form allowed us to gather characteristic information of each patient.

It is made up of 11 parts divided into 2 pages:

- ✓ The first page comprises five parts: (Appendix *Figure 2*)
  - The first part provides information on the identity of the patient, including age, gender and profession.
  - The second part is about the patient's personal history, mainly eventual comorbidities in the form of check boxes.
  - The third part provides information about the date of onset of symptoms and allows to note the date of admission.
  - The fourth part refers to the clinical picture presented by the patient on admission, in the form of check boxes, including the different symptoms of the disease.
  - The fifth part consists of a table listing the items of the biological assessment, obtained during the patient’s check up on admission.

✓ The second page comprises six parts: (Appendix Figure 3)

- The first part relates to paraclinical tests performed on the patient on admission, namely an electrocardiogram, a chest x ray, a CT scan, or any other test.
- The second part is about the classification of the disease, as mild without pneumonia, uncomplicated pneumonia, hypoxemic pneumonia, or severe pneumonia with ARDS.
- The third part lists the various therapeutic modalities available, that the patient benefitted from during his hospitalization, in the form of check boxes.
- The fourth part refers to the evolution of the patient within his hospitalization, with an indication of whether he was admitted to the intensive care unit or not.
- The fifth part concerns the virologic control of the patient, in the form of a table, using RT-PCR on a nasal swab 2 to 4 days apart until negativation, along with serology.
- And finally, the sixth part, which refers to the outcome of the patient, whether he died or was discharged, and allows to note the duration of hospitalization.

III. STATISTICAL STUDY:

- We conducted a statistical study, using the software SPSS (Statistical Package for the Social Sciences, version 25), in order to establish an eventual correlation between clinical and radiological features, and to highlight potential associated factors to both main parameters pre quoted.
- We studied the following variables: age, gender, comorbidities, time to diagnosis, clinical presentation, lung involvement on CT scan, CRP level, LDH level, ferritin level, lymphocytes count, NEWS severity score, and negative PCR on D6 and D8. (Presented in Appendix *Table 3*).
- In the univariate analysis, we used the Khi-2 test to establish a possible link between, on one hand clinical features and all the other variables pre quoted, and on the other hand CT scan features and these variables, considering significant $p < 0.05$.
- In the multivariate analysis, we used binary logistic regression between both clinical and CT scan features, and all the variables whom p was < 0.2 in the univariate analysis.
- Namely, the variables lung involvement and NEWS severity score were not included in the univariate and multivariate, because one of their statistical categories was below 10 individuals, which prevents from an accurate statistical study.

Results

186 patients were selected during the period of our study.

I. AGE

The age of our patients was ranged between 18 and 72 years old (respectively 1.6% and 0.5%). The median age was 34 [27-46.25] years (Appendix *Table 4*).

Table 1: *Distribution of the number of cases according to age groups.*

Age range	Number of patients	Percentage
18 – 24 years	31	16.7%
25 – 39 years	84	45.1%
40 – 64 years	69	37.1%
≥ 65 years	2	1.1%

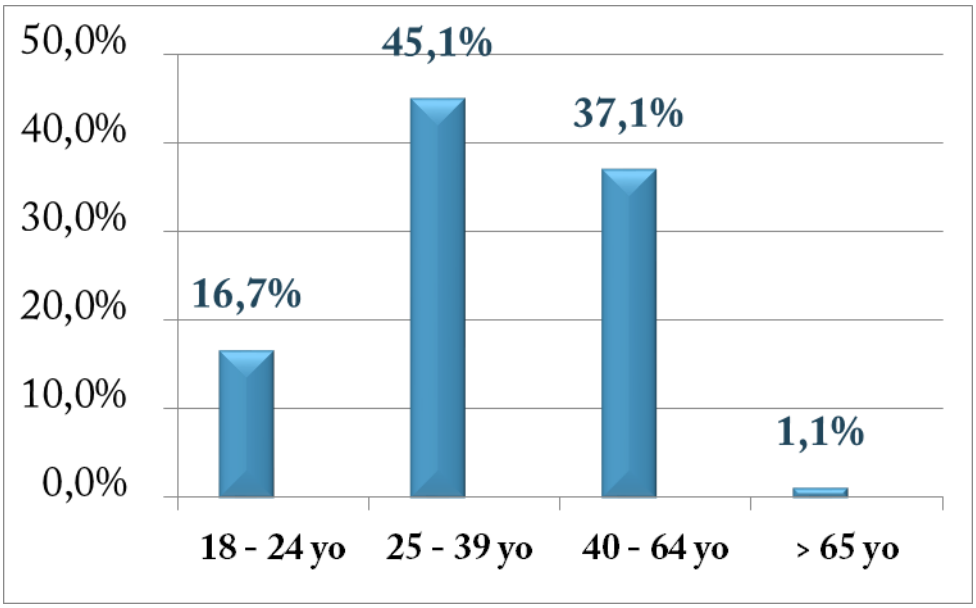


Chart 1: *Distribution of the number of cases according to age groups.*

In our study, most our patients were aged between 25 and 39 years old (45.1%), followed by the age group 40 to 64 years old (37.1%), then 18 to 24 years old (16.7%), and finally the range above 65 years (1.1%).

II. GENDER

We notice a male preponderance of 90.9%, with a sex ratio of 9.94 (Appendix *Table 5*).

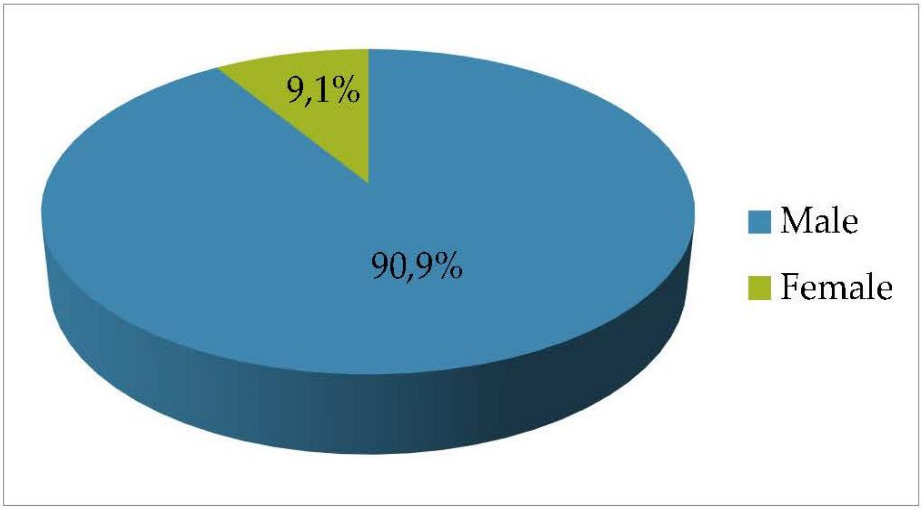


Chart 2: *Distribution of the number of cases according to gender.*

III. COMORBIDITIES

We listed all the pathologies that our patients were suffering from, aside from the COVID-19 infection.

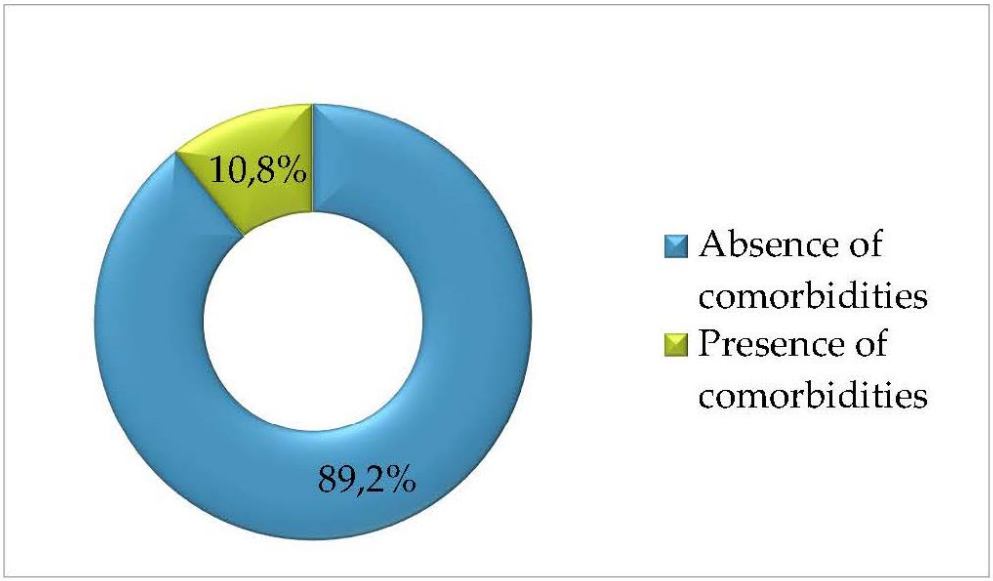


Chart 3: *Rate of comorbidities in 186 COVID-19 patients.*

In our study, only 10.8% had comorbidities, while 89.2% didn't have any underlying chronic pathology (Appendix *Table 6*).

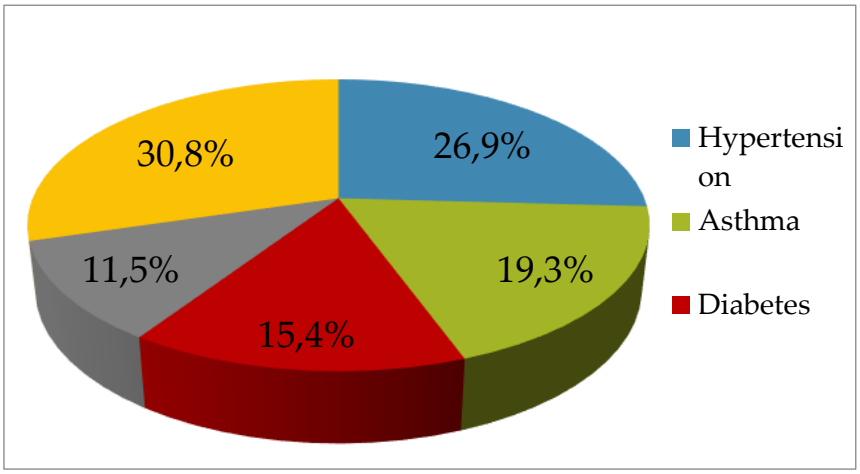


Chart 4: *Distribution of comorbidities in 186 COVID-19 patients.*

20 patients among 186 had comorbidities (10.8%), with hypertension being the most common comorbidity (26.9%), followed by asthma (19.3%), then diabetes (15.4%) and finally heart disease all types included, (11.5%). The remaining patients presented other comorbidities, such as chronic gastritis, chronic sinusitis, anaemia etc…, with a less significant rate.

IV. DIAGNOSIS

A. Diagnosis delay:

Diagnosis delay represents the period between the onset of symptoms and the diagnosis confirmation through RT-PCR at admission.

It is ranged between 1 and 30 days (both less than 3%), with the most frequent delays being 2, 3 and 7 days (respectively 26.7%, 14.7% and 13.7%). (Appendix *Table 7*).

The median diagnosis delay was 4 [2,7] days.

Only 25.3% of the patients had a time to diagnosis exceeding 5 days, against 74.7% patients with less than 5 days.

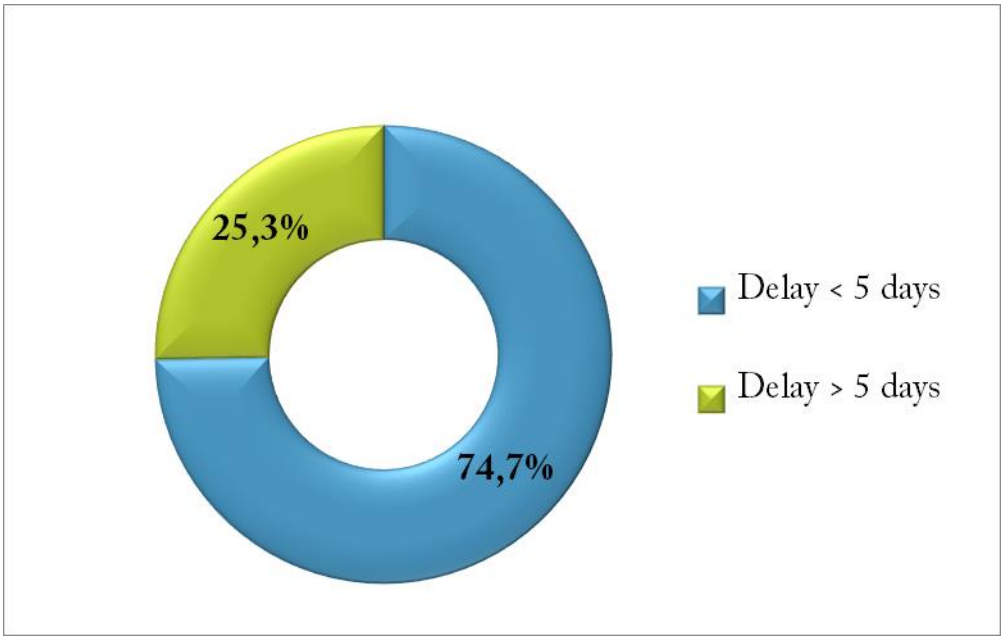


Chart 5: *Distribution of the number of cases according to diagnosis delay.*

B. Clinical:

In our study, the rate of symptomatic patients was 54.8%, against 45.2% asymptomatic.

The distribution of symptoms was as follows:

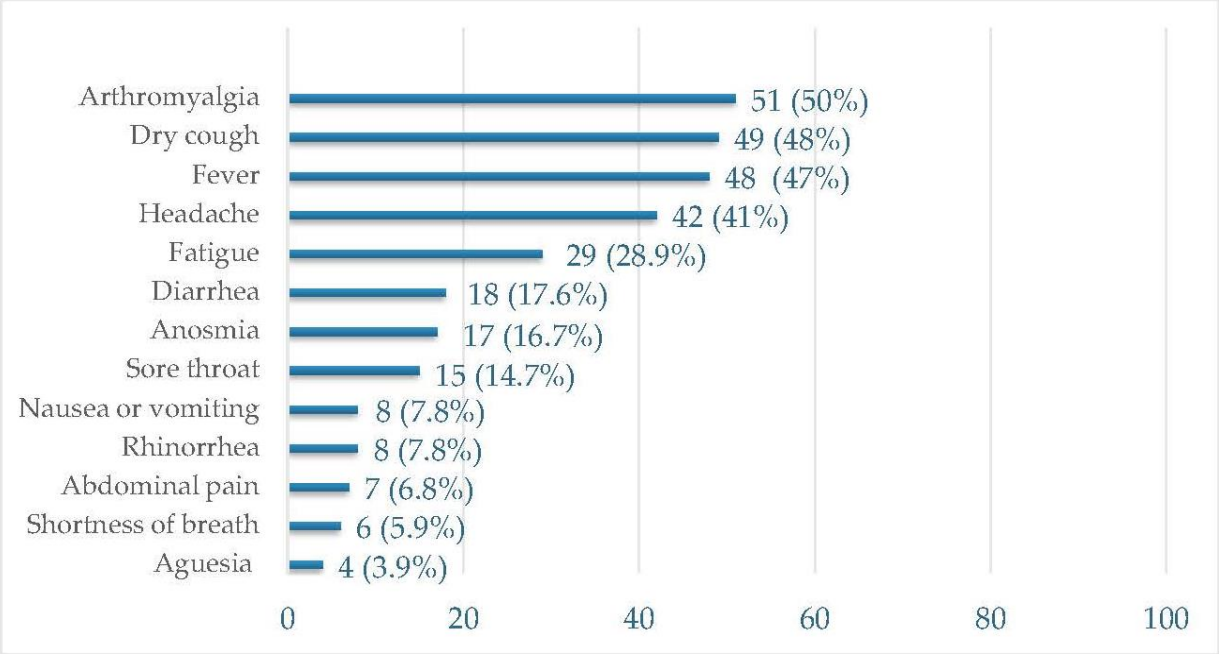


Chart 6: *Ranking of clinical signs according to their frequency in 102 symptomatic COVID-19 patients.*

The symptoms that our patients presented on admission were mainly arthromyalgia (50%), dry cough (48%), fever (47%) and headache (41%), followed by fatigue (28.4%), diarrhea (17.6%), anosmia (16.7%), and sore throat (14.7%), and finally nausea/vomiting and rhinorrhea (respectively 7.8%), abdominal pain (6.8%), shortness of breath (5.9%) and ageusia (3.9%).

Namely, most of our patients (82.4%) presented with two symptoms or more, and so had varied clinical pictures, which explains the distribution of clinical signs.

Furthermore, the most frequent combination of symptoms was fever whether with dry cough, arthromyalgia or headache (14.5%, 13.4%, and 10.8% respectively).

C. Para clinical:

On admission, the patients in our study underwent an RT-PCR to confirm the diagnosis, a complete blood test to highlight potential inflammatory abnormalities, referring to a possibly severe form or one at risk of worsening, and a chest CT scan in order to establish the level of pulmonary involvement and the extent and type of lesions.

1. Molecular diagnosis: Polymerase Chain Reaction

In our study, the RT-PCR was the reference test used to confirm the diagnosis of COVID-19 in all our patients, using a nasal or oropharyngeal swab.

2. Biology

All our patients underwent a full blood screening, based on cell blood count (CBC) with lymphocytes and platelets count, serum electrolytes count, C-reactive protein (CRP), Lactate Dehydrogenase (LDH), ferritin, troponin, liver transaminases, urea, creatinine, and D dimer.

We only collected the data concerning CRP, LDH, Ferritin and lymphocytes count, considering them the main inflammatory markers.

Table 2: *Distribution of the number of cases according to biological disorder.*

Biological disorder	Number of patients	Percentage
Elevated CRP	34	18.3 %
Elevated LDH	46	24.7 %
Elevated Ferritin	25	13.4 %
Lymphopenia	62	33.3 %

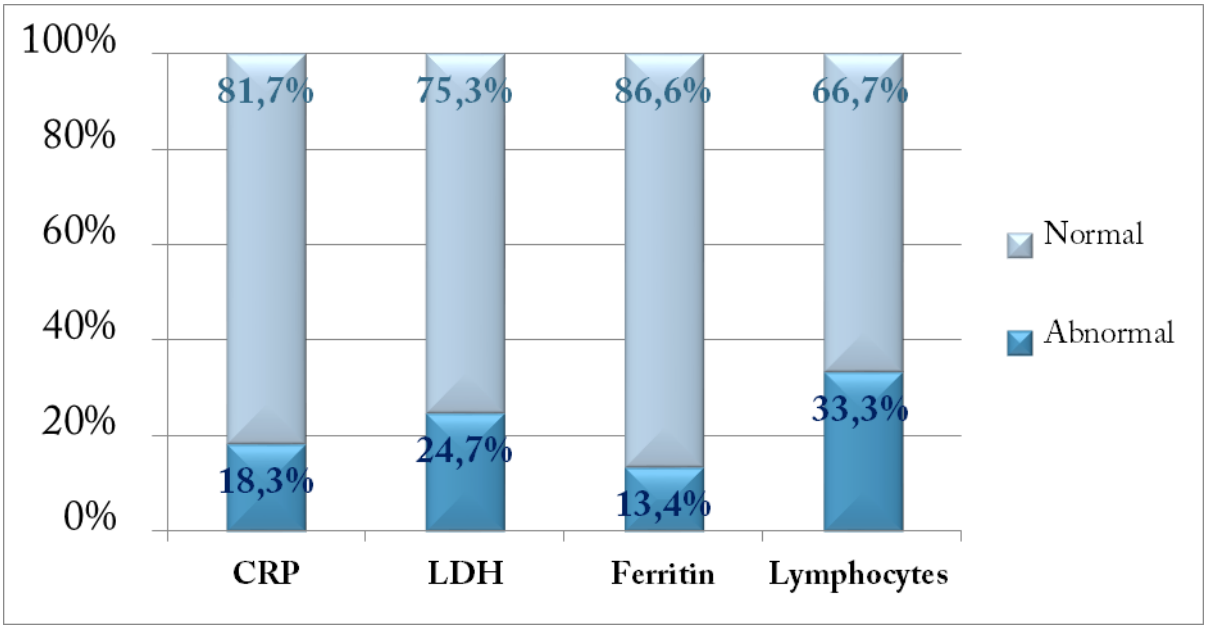


Chart 7: *Rate of biological abnormalities in 186 COVID-19 patients.*

Lymphopenia was observed in 62 cases (33.3%), elevated Lactate Dehydrogenase (LDH) in 46 cases (24.7%), elevated C-reactive protein (CRP) in 34 cases (18.3%), and elevated ferritin was found in 25 cases (13.4%).

3. Imaging:

Chest x ray was not performed routinely because of its low performance.

However, a chest CT scan was performed systematically on admission, in order to strengthen the diagnosis, and to rank the lung damage according to the type of lesions, their location and their extent.

The types of lesions encountered were mainly ground-glass opacities (that was the predominant finding), sometimes in association with consolidation, and a crazy-paving pattern was also found.

Lesions were unilateral or bilateral, central or peripheral, and all lung lobes were likely to be involved.

There were different degrees of extent of the lung lesions, and were ranked in a crescent order as follows: normal (absence of lesions), minimal (< 10% of extension), moderate (10-25%), important (25-50%), severe (50-75%), and critical (> 75%).

Table 3: *Distribution of the number of cases according to the extent of lung injury on chest CT scan.*

Extent of lung injury	Number of patients	Percentage
Normal	99	53.2%
Minimal < 10%	44	23.7%
Moderate 10-25%	29	15.6%
Important 25-50%	11	5.9%
Severe 50-75%	3	1.6%
Critical > 75%	0	0 %

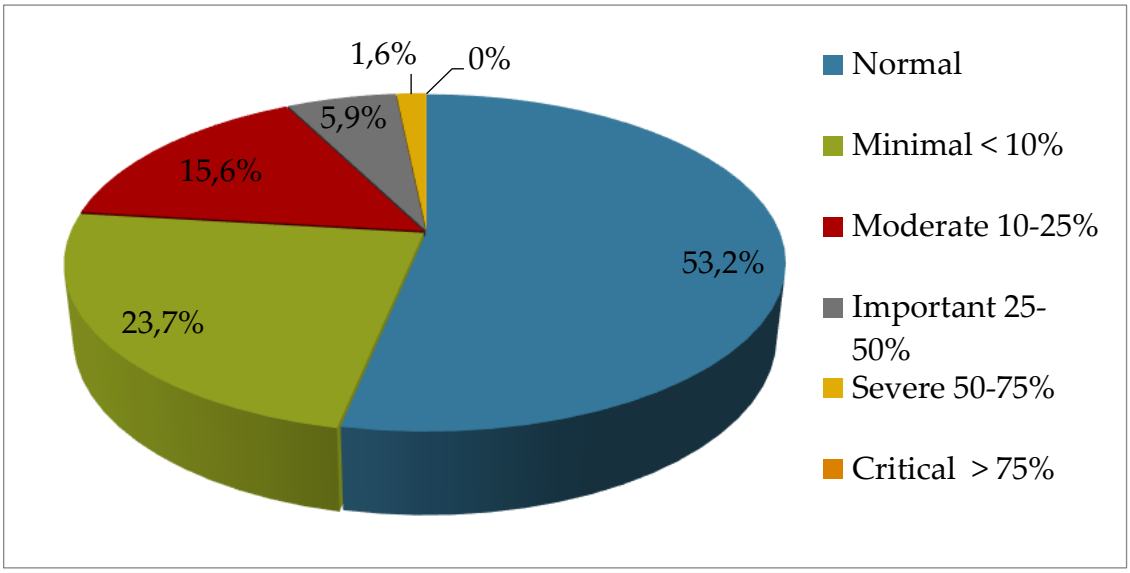


Chart 8: *Distribution of the number of cases according to the extent of lung injury on chest CT scan.*

Nearly half of our patients (53.2%) had a normal CT scan. Within the other half, the most frequent lung extension was minimal (23.7%), followed by moderate (15.6%), then important (5.9%) and finally severe (1.6%). None of our patients had a critical extension of lesions (Appendix *Table 8*).

Besides, all our patients were listed CO-RADS 5.

All the CT scan findings were gathered into a standardized report (*Figure 17*).

ROYAUME DU MAROC
HOPITAL MILITAIRE D'INSTRUCTION
MOHAMMED V
SERVICE D'IMAGERIE MEDICALE
UNITE DE SCANNER

Nom et prénom :
Date : ../../2020

TDM THORACIQUE / COVID 19

- **RC : COVID confirmé**
  - Age :
  - Comorbidités
  - Sx cliniques : Délai des symptômes :
  - Sx de gravité clinique :
  - PCR (+) ; TDM thoracique initiale :

  Technique : Acquisition spiralée sans / avec injection du PCI

- **Résultats :**

1. **Les lésions pulmonaires :**

   * Lésions évocatrices de COVID :

	Verre dépoli	Crazypaving	Condensation	Halo inversé	Lésions fibreuses
Présence	+	+	+		
Lobes atteints	LS, LM, LI				
Topographie des lésions	Unilatérale ☐ Bilatérale ☐ Sous pleurale ☐ Centrale ☐ Mixte ☐				
Etendue des lésions	Minime (< 10%) ☐ Modérée (10-25%) ☐ Etendue (25-50%) ☐ Sévère (50-75%) ☐ Critique (> 75%) ☐				

   * Lésions non COVID :

	Micronodules centro-lobulaires	Condensation systématisée	Cavitation	Masse	Sécrétions endo-bronchiques
Présence	-	-	-	-	-
Lobes atteints					

   * Poumon sous-jacent : Emphysème ☐ Fibrose ☐ Autre ☐

2. **Les anomalies pleurales :** Pneumothorax ☐ Pleurésie ☐ Calcification ☐
3. **Les anomalies médiastinales :** ADP ☐ Artères pulmonaires ☐ Aorte ☐
4. **Lésions osseuses : RAS**
5. **Lésions abdominales hautes : RAS**

- **CONCLUSION**

Signé : DR ……

Figure 17: *typical CT scan report.*

V. TREATMENT

In our study, all the patients benefitted from the national protocol associating hydroxychloroquine and azithromycin (Appendix *Figure 4*), along with supportive care, such as oxygen therapy, vitamin therapy, with potentially adding antibiotic therapy (bases on beta-lactam; either amoxicillin or 3d generation cephalosporins) and/or antiviral treatment (based on lopinavir/ritonavir) when needed; i.e. noticing clinical and/or biological signs suggesting a superinfection or progression, and adding anticoagulant treatment based on low molecular weight heparin (LMWH) in case of biological coagulation disorder (elevated d-dimer) alongside with lung lesions in CT Scan.

VI. PROGNOSIS

We studied the prognosis of our patients using the NEWS severity score.

Table 4: *NEWS Classification severity score* **[149]**.

Groups	**Definition**
Asymptomatic	Lack of clinical signs.
Mild	Symptoms of a pulmonary infection without pneumonia signs.
Moderate	Presence of pneumonia with no signs of severity, or mild form but with risk factors.
Severe	Signs of severity not requiring intubation.
Critical	Need for ventilatory assistance with intubation.

Table 5: *Distribution of 186 COVID-19 patients according to NEWS Classification.*

Groups	Number of patients	Percentage
Asymptomatic	84	45.2 %
Mild	35	18.8 %
Moderate	62	33.3 %
Severe	5	2.7 %
Critical	0	0 %

84 patients (45.2%) were asymptomatic, 35 (18.8%) were mild, 62 (33.3%) were moderate, 5 (2.7%) cases were severe, and none of our patients belonged to the critical group (Appendix *Table 9*).

VII. EVOLUTION AND OUTCOME

All our patients recovered completely and were discharged.

The clinical cure, retained on the disappearance of clinical symptoms and apyrexia for more than 3 days, after 2 weeks of well conducted treatment, was obtained in 184 patients representing 98.9% of the study population.

51 patients (27.4%) had an early virologic clearance, as in they were tested negative on the 6th and 8th day respectively, while 135 patients (72.6%) were not, and kept being tested until negativity, 4 days apart (Appendix *Table 10*).

The longest hospitalization duration was 38 days.

7 patients required oxygen therapy (3.8%), and 1 patient (0.5%) was transferred to intensive care unit for 48 hours, and was discharged afterwards.

No deaths were reported.

In some patients randomly chosen, with different lung involvements initially, control CT scan 3 months afterwards found a complete disappearing of the lung lesions with a full radiological cleaning.

Discussion

Our study reports the results of the initial management of the patients admitted to the Center for Virology, Infectious and Tropical Diseases (CV MIT) during the containment period.

186 patients were collected during the first two months, between March and May 2020.

I. AGE

The median age of our patients was 34 years [27-46.25] (range 18-72).

In a study conducted in two west African countries, Guinea and Burkina Faso, between March and November 2020 by ***Jaspard*** *et al.*, including 1805 cases with a positive SARS-CoV-2 test on nasopharyngeal swab, the median age was 41 years [30–57] (range 1–99 years) **[150]**.

According to ***Richardson*** *et al.*, in their study conducted in hospitals in Northwell Health in New York City area, USA, between March 1st and April 4th, 2020, including 5700 patients with confirmed SARS-CoV-2 infection by positive result on PCR testing of a nasopharyngeal sample, the median age was 63 years [52-75] (range 0-107 years) **[151]**.

In a study conducted in the UK by ***Docherty*** *et al.*, including 20133 patients with a positive RT-PCR between 6 February and 19 April 2020, the median age was 73 years [58, 82] (range 0-104) **[152]**.

And according to ***Zhou*** *et al.*, in their study including 191 patients admitted to Jinyintan Hospital and Wuhan Pulmonary Hospital in China as of 31th January, 2020, the median age was 56 years [46-67] (range 18-87) **[153]**.

These age variations can be explained by the fact that all positive patients during this period were admitted to the hospital, the test-track-isolate principle was adopted regardless of the clinical picture, whereas in western countries, particularly the UK and the USA, only patients with severe criteria were hospitalized, and most of them were elderly or had comorbidities.

II. GENDER

Most cohorts have a male preponderance of approximately 60%.

Our study found a male preponderance of 90,9%.

In the African study, 64% were men and 36% women **[150]**.

The US study found 60.3% of men and 39.7% of women **[151]**.

In the UK study, 60% were men and 40% were women **[152]**.

In the Chinese study, 62% were men, and 38% were women **[153]**.

The increase in our rate can be explained by the fact that our study took place in a military institution, characterized by a predominantly male population.

III. COMORBIDITIES

In our study, only 10.8% of the patients had comorbidities, while 89.2% didn’t have any underlying chronic pathology.

Hypertension was the most common comorbidity (26.9%), followed by asthma (19.3%), then diabetes (15.4%) and finally chronic heart disease all types included (11.5%). Chronic kidney disease, chronic liver disease and malignancy were not found in our patients’ medical history.

Current evidence from China and the US suggests that comorbidities such as hypertension, diabetes, obesity, chronic obstructive pulmonary disease and cerebrovascular disease increase the risk of severity and death from COVID-19 **[154][155][156][157]**.

In a study conducted in Nigeria between February 27th and July 6st, 2020, by ***Osibogun*** *et al.,* including 2184 patients tested positive COVID-19, 22.5 % had comorbidities, with hypertension being the most common comorbidity (74.2%), diabetes (30.3%), asthma (10.2%), chronic heart disease (2.9%), malignancy (2.9%), chronic kidney disease (1.8%), chronic liver disease (1.8%) **[158]**.

According to ***Richardson*** *et al.,* 94.3% of the patients had comorbidities, with the most common being hypertension (56.6%), obesity (41.7%), and diabetes (33.8%), chronic heart disease (18%), asthma (9%), chronic kidney disease (8.5%), malignancy (6%), and chronic liver disease (0.6%) **[151]**.

In another study conducted in 14 states in the United States between March 1st and 28th, 2020, by ***Garg*** *et al.,* including 1482 patients hospitalized with COVID-19, 89.3% had comorbidities, with hypertension being the most common comorbidity (49.7%), obesity (48.3%), diabetes (28.3%), chronic heart disease (27.8%), asthma (17%), chronic kidney disease (13.1%), chronic liver disease (6.6%) **[159]**.

And according to ***Zhou*** *et al.,* comorbidities were present in nearly half of the patients (48%), with hypertension being the most common comorbidity (30%), followed by diabetes (19%) and coronary heart disease (8%), obstructive lung disease (3%) malignancy (1%), chronic kidney disease (1%) **[153]**.

Table 6: *Comparison of comorbidities rate in our study with published literature.*

	Osibogun *et al.* **[158]**	***Richardson*** *et al.* **[151]**	***Garg*** *et al.* **[159]**	***Zhou*** *et al.* **[153]**	*Our study*
Presence of comorbidities	22.5%	94.3%	89.3%	48%	10.8%
Hypertension	74.2%	56.6%	49.7%	30%	26.9%
Diabetes	30.3%	38.3%	28.3%	19%	15.4%
Heart disease	2.9%	18%	27.8%	8%	11.5%
Asthma	10.2%	9%	17%	3%	19.3%
Obesity	-	41.7%	48.3%	-	-
Chronic kidney disease	1.8%	8.5%	13.1%	1%	0%
Malignancy	2.9%	6%	-	1%	0%
Chronic liver disease	1.8%	0.6%	6.6%	-	0%

The rate of comorbidities is different, which can be explained by the fact that our study took place in a military institution, characterized by a population supposedly without any health conditions diagnosed beforehand, and also by the fact that all positive patients were admitted to the hospital during this period.

In spite of that, we notice that the principal comorbidities associated to COVID-19 infection are hypertension being the most common, then diabetes asthma and heart disease, with a slight variation in their ranking. Then less frequently encountered comorbidities, that were not considered systematically in all the studies, i.e., malignancy, chronic kidney and chronic liver diseases.

➲ ***Comorbidities and disease severity***

The disease severity and improvement were defined according to the interim guidelines from the World Health Organization and the National Health Commission of China. According to the patients' symptoms, laboratory results and imaging findings at admission, the disease severity of COVID-19 patients can be divided into four types: mild, moderate, severe, and critical.

- **Mild** = slight clinical symptoms without imaging findings of pneumonia
- **Moderate** = fever or respiratory symptoms
- **Severe** = respiratory distress and a respiratory rate > 30 times per minute, fingertip blood oxygen saturation < 93% at rest, and partial arterial oxygen pressure (PaO2)/fraction of inspiration oxygen (FiO2) < 300 mmHg
- **Critical** = one of the following:
  - Respiratory failure requiring mechanical ventilation
  - Shock condition
  - Other organ failure necessitating ICU treatment.
  - Acute kidney injury diagnosed according to the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines.
  - Acute respiratory distress syndrome (ARDS) diagnosed according to the Berlin definition **[160]**.

Table 7: *Comorbidities distribution within severity conditions, according to* ***Zhang J*** *et al.* **[160]**.

	n = 663 (%)	**Comorbidities**	**No comorbidities**
Mild	3 (0.5%)	0%	100%
Moderate	251 (37.8%)	23.5%	76.5%
Severe	315 (47.5%)	40%	60%
Critical	94 (14.2%)	66%	34%

It has been reported that patients with comorbidities, such as cardiovascular disease, diabetes, arterial hypertension, chronic lung disease, cancer (particularly hematologic neoplasms, lung cancer and metastatic disease), chronic kidney disease, obesity and smoking, are more likely to develop a severe disease **[134]**.

IV. DIAGNOSIS

COVID-19 diagnosis is typically based on polymerase chain reaction testing performed on a nasal swab. However, because of the rate of false negative test results of the PCR, clinical, laboratory, and imaging findings should also be used in conjuncture to make a supposed diagnosis **[11]**.

A. Diagnosis delay:

The median diagnosis delay identified in our study was 4 [2,7] days **[161]**. Based on the epidemiological survey of the center for disease control in China, the incubation period for SARS-CoV-2 is 1-14 days **[162]**.

According to ***Guan*** *et al.*, the median incubation period was 4 days [2,7] **[163]**.

The median interval from symptom onset to hospital admission was 7 [3-9] days in ***Garg*** *et al.* study **[159]**, while it was 4 [1, 8] days according to ***Docherty*** *et al*. **[152]**.

Our findings are similar to the first published data on the disease.

B. Clinical:

COVID-19 has various clinical manifestations. The infection may result in asymptomatic manifestations, or it may lead to a wide spectrum of symptoms, from mild signs of upper respiratory tract infection to life-threatening sepsis **[11]**.

In our study, 84 patients were asymptomatic, which represented 45.2% of the SARS-CoV-2 infections.

In the symptomatic group (54.8%), the symptoms that our patients presented on admission were mainly arthromyalgia (50%), dry cough (48%), fever (47%) and headache (41%), followed by fatigue (28.4%), diarrhea (17.6%), anosmia (16.7%), and sore throat (14.7%), and finally nausea/vomiting and rhinorrhea (respectively 7.8%), abdominal pain (6.8%), shortness of breath (5.9%) and ageusia (3.9%).

According to ***Oran*** *et al.*, in their literature review of 16 cohorts about the prevalence of asymptomatic SARS-CoV-2 infection, from April 19 through May 26 2020, asymptomatic patients seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days **[164]**.

Table 8: *Summary of SARS-CoV-2 testing studies* **[164]**.

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* An en dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

Symptomatic patients usually present with systemic and/or respiratory symptoms, yet it has been reported that gastrointestinal, cardio vascular and, less commonly, dermatological and neurological symptoms can also occur.

The symptomatology of COVID-19 is non-specific and cannot be clinically distinguished from other viral respiratory infections, though the occurrence of dyspnea several days after the onset of symptoms is suggestive of a SARS-COV-2 infection **[165][166]**. The most common associated symptoms include: cough (50%), subjective fever or fever higher than 38°C (43%), myalgia (36%), headache (34%), dyspnea (29%), sore throat (20%), diarrhea (19%), nausea/vomiting (12%), abdominal pain, runny nose, anosmia and ageusia (<10% respectively) **[165-167]**. Gastrointestinal symptoms are less common, though they may be the initial symptoms, ands skin alterations similar to erythema pernio have also been reported, especially in the fingers and toes. **[168]**.

➲ ***Spectrum of severity***

Patients with mild disease only present with low fever and slight asthenia, without pneumonia. In severe cases, dyspnea and/or hypoxemia usually occur one week after disease onset **[167]**, and rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, bleeding, and coagulation dysfunction, that are difficult to cure, and need ventilatory support and intensive care unit (ICU) admission **[134][161]**.

In study conducted in China, about 44,500 COVID-19 patients, 81% had a mild disease, while 14% had severe illness and 5% were critically ill **[169]**.

And in a study of 2741 hospitalized patients, 24% died and 27% required intensive care, of which 60% died **[170]**.

Table 9: *Literature review summary: Studies that demonstrated signs and symptoms characteristics of COVID-19 pneumonia* **[171]**, *in comparison with our study.*

Author(s)	***Huang** et al.*	***Chen** et al.*	***Shi** et al.*	***Guan** et al.*	***Zhou** et al.*	***Wang** et al.*	***Xu** et al.*	***Yang** et al.*	***Rodriguez** et al.*	**WHO report**	***Cao** et al.*	***Yin** et al.*	Our study
No. of study	1	1	1	1	1	1	1	1	19		31	1	1
Patient volume	41	99	81	1099	62	138	90	149	9-1590		10-1099	2126	186
Name Location of institution(s)	China Medical Treatment Expert Group for COVID-19	Wuhan Jinyintan Hospital	Union Hospital, - University of Science & Technology (Wuhan)	China Medical Treatment Expert Group for COVID-19	-Hospital, - University of Science & Technology (Wuhan)	Zhongnan Hospital, Wuhan University	1st Hospital of Jinan University, Guangzhou 8th People's Hospital	Ruijin Hospital Shanghai Jiaotong University	Latin American Network of COVID-19 Research	WHO-China Joint Mission on COVID-19	Union Hospital, - University of Science & Technology (Wuhan)	-Hospital, - University of Science & Technology (Wuhan)	Mohammed V Military Teaching Hospital (Rabat)
Time by (of) study	2020/1/2	2020/1/20	2020/1/23	2020/1/29	2020/1/30	2020/2/3	2020/2/4	2020/2/10	2020/2/23	2020/2/24	2020/3/1	2020/4/8	2020/6/16
Fever	**98%**	**83%**	**73%**	43.8%	**87.10%**	**98.6%**	**78%**	**76.51%**	**88.7%**	**88%**	**87.3%**	**90.92%**	47%
Dry cough	76%	82%	59%	**67.8%**	45.16% [b]	59.4%	63%	58.39%	57.6%	68%	58.1%	62.46%	48%
Fatigue	44% [a]		5%	38.1%	22.58%	69.6%	21%		29.4% [d]	38%	35.5% [e]	43.74%	28.4%
Sputum production	28%		19%	33.7%		26.8%	12%	32.21%	28.5%	33%	29.4%	37.44%	
Shortness of breath	55%	31%	42%	18.7%	24.19%	31.2%		1.34%	45.6%	19%	38.3%	25.87%	5.9%
Chest tightness		2%	22%					14.10%	45.6%		31.2%	22.11%	
Muscle or joint pain		11%		14.9%	32.26%	34.8%	28%	3.36%		15%		19.99%	**50%**
Headache	8%	8%	6%	13.6%		6.5%	4%	8.72%	8%	14%	9.4%	12.51%	41%
Diarrhea	3%	2%	4%	3.8%	14.52% [c]	10.1%	6%	7.38%	6.1%	4-31%	6.8%	11.10%	17.6%
Chills				11.5%			7%	14.09%		11%		9.97%	
Anorexia			1%			39.9%						9.83%	
Nausea or vomiting		1%	5%	5%		13.7%	8%	1.34%		5%		8%	7.8%
Dizziness		9%	2%			9.4%						7.01%	
Abdominal pain						2.2%						5.93%	6.8%
Hemoptysis	5%			0.9%						0.9%		1.03%	
Loss of smell										15-30%			16.7%
Sore throat		5%		13.9%		17.4%	26%	14.09%	11%	14%	12%		14.7%
Nasal congestion		4%	26%	4.8%				3.36%		5%			7.8%
Conjunctival congestion				0.8%									
Pink eyes										0.8%			

a Fatigue or myalgia. b Cough & sputum. c Abdominal pain or diarrhea. d Fatigue or myalgia. e Fatigue or myalgia

C. Paraclinical:

1. Molecular diagnosis: Polymerase Chain Reaction

SARS-CoV-2 RNA detection using reverse transcription polymerase chain reaction from respiratory samples (e.g., nasopharynx) is the standard tool for diagnosis **[11]**. However, the sensitivity of testing varies within timing of testing relative to exposure. One modeling study estimated sensitivity at 33% 4 days after exposure, 62% on the day of symptom onset, and 80% 3 days after symptom onset **[172-174]**. Factors contributing to false-negative test results include the suitability of the sample collection technique, time from exposure, and the sample origin. Lower respiratory samples, such as bronchoalveolar lavage fluid, are more sensitive than upper respiratory samples.

All patients included in our study were tested positive by RT-PCR, based on nasal or pharyngeal swab specimen, within their hospital admission.

***Wang** et al.* conducted a study about detection of SARS-CoV-2 in various types of clinical specimens, collected based on clinical indications from 3 hospitals in China, from January 1st through February 17th, 2020. Pharyngeal swabs were collected from most patients 1 to 3 days after hospital admission. Blood, sputum, feces, urine, and nasal samples were collected throughout the illness. Bronchoalveolar lavage fluid and fibro bronchoscope brush biopsy were sampled from patients with severe illness or undergoing mechanical ventilation. 1070 specimens were obtained from 205 patients, and among them, broncho alveolar lavage fluid specimens had the highest positive rates of SARS-CoV-2 PCR testing results (93%), followed by sputum (72%), nasal swabs (63%), and pharyngeal swabs (32%). SARS-CoV-2 can also be detected in feces, but not in urine **[172]**.

Saliva is an interesting alternative specimen source, that requires less personal protective equipment and fewer swabs, but needs further validation **[175]**.
Hence, RT-PCR results must be combined with other detection results and clinical characteristics in order to make a better diagnosis, **[176]**.

2. Antigenic test

At the moment of our study, antigenic testing devices were not available and so not used for a fast diagnosis purpose. The first use was by November 2020.
Instead, all our patients' diagnosis was confirmed using RT-PCR.
In a study conducted by ***Kahn*** *et al.*, between June 23^{d} and November 26th, 2020 in Germany, a total of 3630 antigen tests were performed, 3110 had a concomitant nucleic acid amplification tests (NAAT) result. Of these, 96 samples (3.1%) were positive by NAAT. 57 (59.4%) of the NAAT-positive samples were also positive by antigen test (*Table 10*) **[131]**.
Thus, diagnosis sensitivity and specificity of the point-of-care antigen test (AgPOCT) were 59.4% and 99.0%, respectively, compared to NAAT. Given a calculated prevalence of 3% in the study population, negative and positive predictive values were 98.7% and 64.8%, respectively (*Table 10*).
Among 2589 tests performed in the emergency department, 249 (9.6%) were from patients with clinical symptoms consistent with COVID-19 disease (*Table 10*).
In symptomatic patients, sensitivity of antigen tests compared to NAATs is higher than in asymptomatic patients (66.7% vs. 47.6%). The calculated prevalence was 16% and 1.9% in symptomatic and asymptomatic patients, respectively. This results in a PPV of 85% in Ag-positive symptomatic patients compared to 44.4% in asymptomatic controls. Consistently, diagnosis specificity (98.9% and 97.0%) and negative predictive values (99.0% and 91.9%) are lower in symptomatic patients than in asymptomatic controls (*Table 10*) **[131]**.

Table 10: *Point-of-Care test results of AgPOCT compared to NAAT of samples tested within 24 hours.*

SARS-CoV2	Entire cohort		Asymptomatic patients		Symptomatic patients	
	Ag positive	Ag negative	Ag positive	Ag negative	Ag positive	Ag negative
NAAT positive	57	39	20	22	34	17
NAAT negative	31	2983	25	2273	6	192
Sensitivity (%)	59.4		47.6		66.7	
Specificity (%)	99.0		98.9		97.0	
PPV (%)	64.8		44.4		85.0	
NPV (%)	98.7		99.0		91.9	

3. Biology

In our study, the most frequent biological abnormality was lymphopenia with a rate of 33.3%, against 66.7% of the patients whom lymphocytes count was normal. Secondly, elevated Lactate Dehydrogenase (LDH) was found in 24.7% of the patients, against 75.3% with normal LDH. In the third place, elevated C-reactive protein (CRP) was encountered in 18.3%, against 81.7% with normal CRP. And finally, 13.4% of the patients had an elevated ferritin, against 86.6% with normal ferritin.

A systematic review of 19 studies of 2874 patients, mostly from China, of whom 88% were hospitalized, reported the typical panel of biological abnormalities seen in COVID-19, namely elevated serum C-reactive protein (over 60% of patients), increased lactate dehydrogenase (approximately 50%-60%), alanine aminotransferase (elevated in approximately 25%), and aspartate aminotransferase (increased in approximately 33%) **[177]**. Lymphopenia is the most frequent hematological disorder encountered (with an absolute lymphocyte count < 1.0×10^9/L), and it is found in up to 83% of hospitalized patients. Also, modest prolongation of prothrombin time (> 5% of patients), mild thrombocytopenia (about 30% of patients) and elevated D-dimer

values (43%-60% of patients) are commonly seen. However, most of these biological abnormalities are nonspecific and quite common in pneumonia **[11]**.

➲ ***Biology features and disease severity***

More severe biological disorders have been observed in patients with severe and critical conditions **[11]**. D-dimer, and to a lesser extent, lymphopenia appear to have the most significant prognosis associations, according to ***Wu*** *et al.*, in a Chinese study about 201 patients **[178]**.

It has also been reported that the plasma levels of interluekin-2 (IL-2), IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon induced protein-10 (IP10), monocyte chemo-attractant protein-1 (MCP-1), macrophage inflammatory protein 1alpha (MIP1A), and tumor necrosis factor alpha (TNF alpha) levels in ICU (Intensive Care Unit) patients were higher than those of non-ICU patients, and initial plasma levels of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor (FGF), G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon gamma (IFN gamma), IP10, MCP1, MIP1A, MIP1B, platelet derived growth factor (PDGF), TNF alpha, and vascular endothelial growth factor (VEGF) were higher in both ICU patients and non-ICU patients, when compared to that in healthy individuals **[179-181]**.

Table 11: *Comparison of biological abnormalities rate in our study with published literature.*

		Wu *et al.* **[178]**	***Zhang*** *et al.* **[160]**	***Richardson*** *et al.* **[151]**	*Our study*
Laboratory abnormalities	Elevated CRP	85.6%	58.5%	79.2%	18.3%
	Elevated LDH	68.2%	48.3%	70.2%	24.7%
	Elevated ferritin	-	-	76.2%	13.4%
	Lymphopenia	64%	51%	59.4%	33.3%

This table highlights the proportion of biological disorders in our series compared to other studies, where we notice the same abnormalities despite the disparity in their distribution.

4. Imaging

The standard test for the SARS-CoV-2 detection is RT-PCR, usually performed on a nasopharyngeal or respiratory secretion sample. It is believed to be highly specific, but its sensitivity can range from 60-70% to 95-97% **[182][183]**, since it varies according to time since exposure to the virus, so false negatives are a real clinical problem **[175]**.

Imaging tests have a major role in the diagnosis and management of patients, and are mainly used to help diagnose the disease, determine its severity, guide treatment, and assess response to treatment. The current recommendation of the most of scientific and radiological associations is to not consider imaging tests

as screening tools for COVID-19. Instead, they should be dedicated to the evaluation of complications **[184]**.

a) Chest X-ray

Our patients didn't benefit from the chest X ray, they directly underwent a chest CT scan, because of its better performance.

In mild cases or early-stage disease, chest X-ray findings may be normal. However, patients with moderate to severe symptoms are more likely to have an abnormal chest radiography **[135][185]**.

A Chinese study including patients with COVID-19 confirmed by using RT-PCR and chest radiographic between January and March, 2020, conducted by ***Wong*** *et al.*, found that most imaging findings are pathological in the patients requiring hospitalization (69% at admission and 80% afterwards). And findings are more evolved with a bigger extent 10 to 12 days after the first symptoms. The most prevalent findings are airspace opacities, which may be consolidations or, less frequently, ground-glass opacities **[135]**.

Chest X-ray findings in patients with suspected COVID-19 have been divided into four categories to help facilitate diagnosis **[139][185-187]**:

- ***Normal chest X-ray:*** It is very common for the chest X-ray to be normal in early-stage disease, so a normal chest radiography does not rule out infection **[135][185]**.

- ***Typical findings*** or ***findings commonly associated with COVID-19 in the scientific literature*** (*Figure 18*): Comprising a reticular pattern, ground-glass opacities and consolidations, with rounded morphology and a confluent or patchy multifocal distribution. The pattern is typically bilateral and peripheral, with a predilection for the lower fields **[135]** (*Figure 18*).
- ***Indeterminate findings*** and findings that may occur in COVID-19 pneumonia may have other causes. These are notably consolidations and ground-glass opacities, with a unilateral, central or upper-lobe pattern (*Figure 19A*). **[134]**.
- ***Atypical***, ***uncommon*** or ***unreported findings in COVID-19 pneumonia***. These include lobar consolidation, miliary pattern, lung nodules or masses, cavitation and pleural effusion, reported in only 3% of the cases, and are more commonly encountered in advanced disease (*Figure 19B and C*) **[135]**.

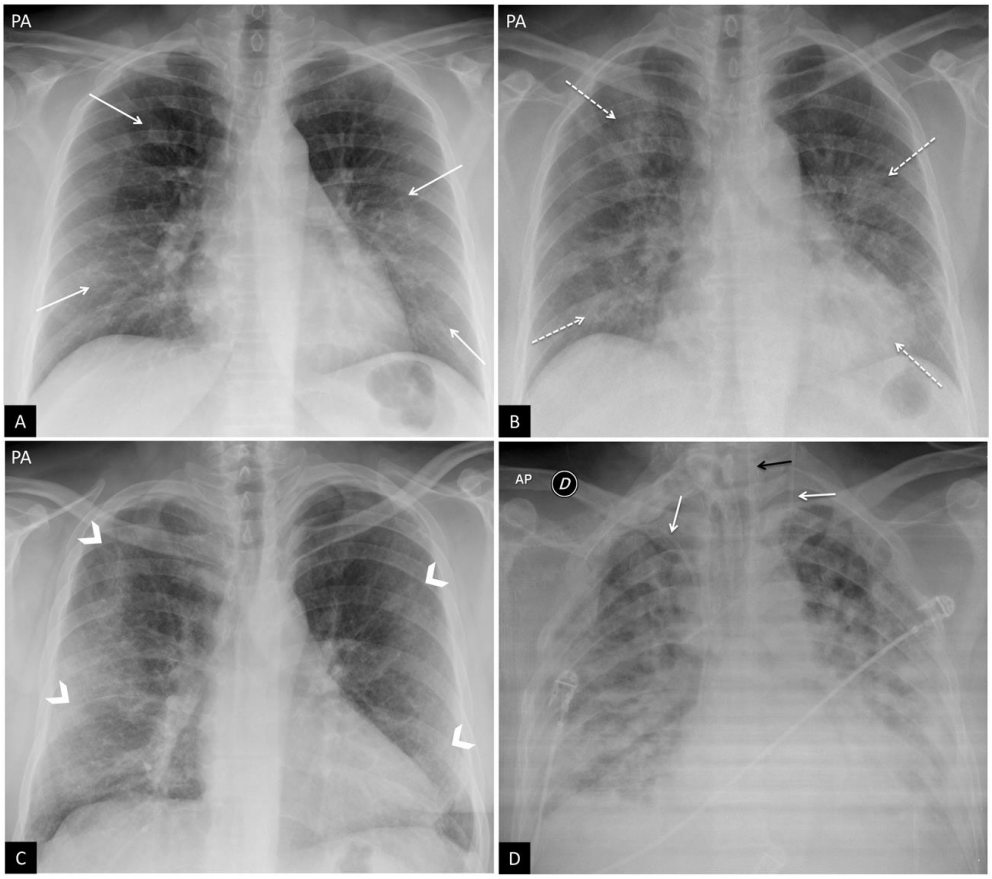


Figure 18: *Typical findings in COVID-19 pneumonia* **[134]**.

(A) A 47-year-old woman with symptoms raising suspicion of COVID-19. Posteroanterior (PA) chest X-ray. Reticular interstitial pattern with peripheral predominance (arrows).

(B) Same patient as in image A. PA chest X-ray taken 3 days later. Positive PCR for SARS-CoV-2. Despite being taken with poorer inspiration. the X-ray shows faint rounded bilateral peripheral alveolar opacities (dotted arrows).

(C) A 57-year-old male with dyspnea and positive PCR for SARS-CoV-2. Bilateral peripheral opacities in upper, middle and lower fields (arrow tips).

(D) A 45-year-old male with dyspnea and COVID-19 confirmed by PCR. Antero posterior chest X-ray showing multiple bilateral diffuse confluent areas of consolidation with extensive involvement of both lungs. There is a presence of two central venous lines, one left jugular and the other right subclavian (white arrows), and a gastrointestinal tube (black arrow).

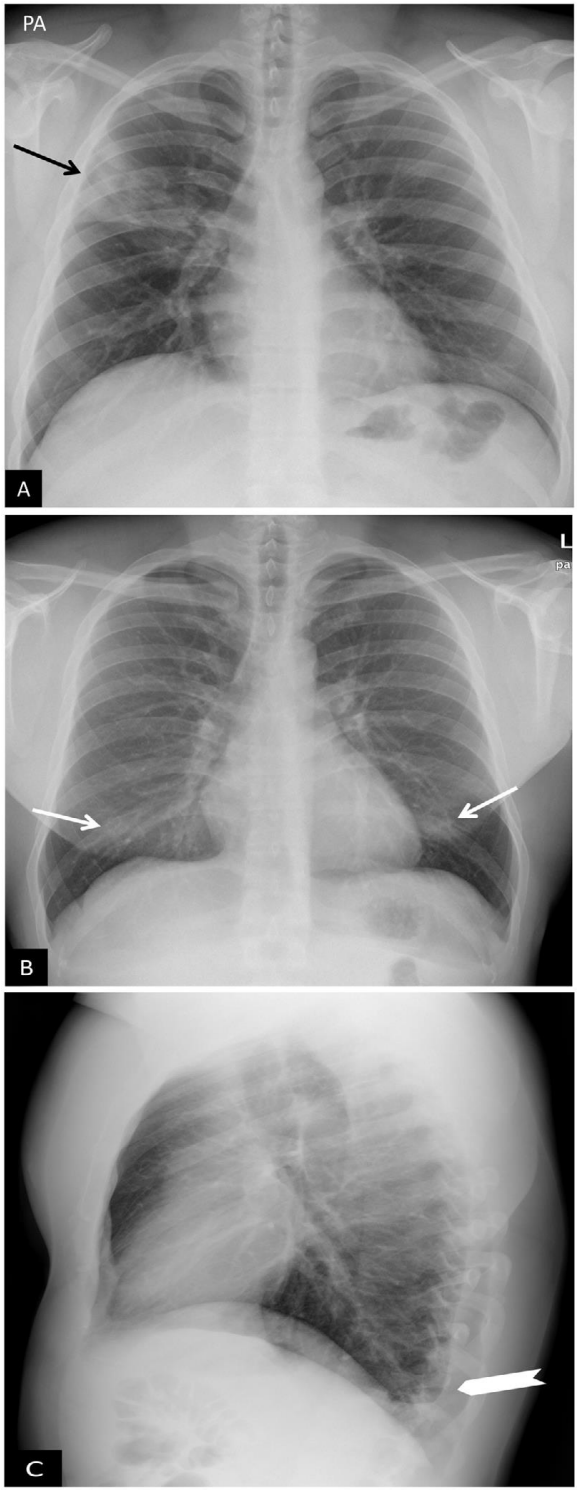


Figure 19: *Atypical findings in COVID-19 pneumonia* **[134]**.

(A) ***Lobar pneumonia***. A 28-year-old male patient with symptoms consistent with COVID-19 and positive PCR for SARS-CoV-2. Chest X-ray in posteroanterior (PA) projection. Right upper lobe involvement (arrow).

(B and C) ***Bilateral involvement and pleural effusion***. A 17-year-old male patient with fever and positive PCR for SARS-CoV-2. PA **(B)** and lateral **(C)** chest X-ray. Faint bilateral infiltrates in lower fields (arrows) with minimal pleural effusion in the left posterior costo-diaphragmatic sinus (arrow tip).

b) CT scan

In our study, a chest CT scan was performed systematically on admission, in order to strengthen the diagnosis, and to rank the lung damage according to the type of lesions, their location and their extent.

⇒ Type of lesions: the types of lesions encountered were mainly ground-glass opacities (that was the predominant finding), sometimes in association with consolidation, and a crazy-paving pattern was also found.

⇒ Location: lesions were either unilateral or bilateral, central or peripheral, and all lung lobes were likely to be involved.

⇒ Extent: there were different degrees of extent of the lung lesions, and were ranked in a crescent order as follows: normal (absence of lesions), minimal (< 10% of extension), moderate (10-25%), important (25-50%), severe (50-75%), and critical (> 75%).

Table 12: *Distribution of the number of cases according to extent of lung injury on chest CT scan.*

Extent of lung injury	Number of patients	Percentage
Normal	99	53.2%
Minimal < 10%	44	23.7%
Moderate 10-25%	29	15.6%
Important 25-50%	11	5.9%
Severe 50-75%	3	1.6%
Critical > 75%	0	0 %

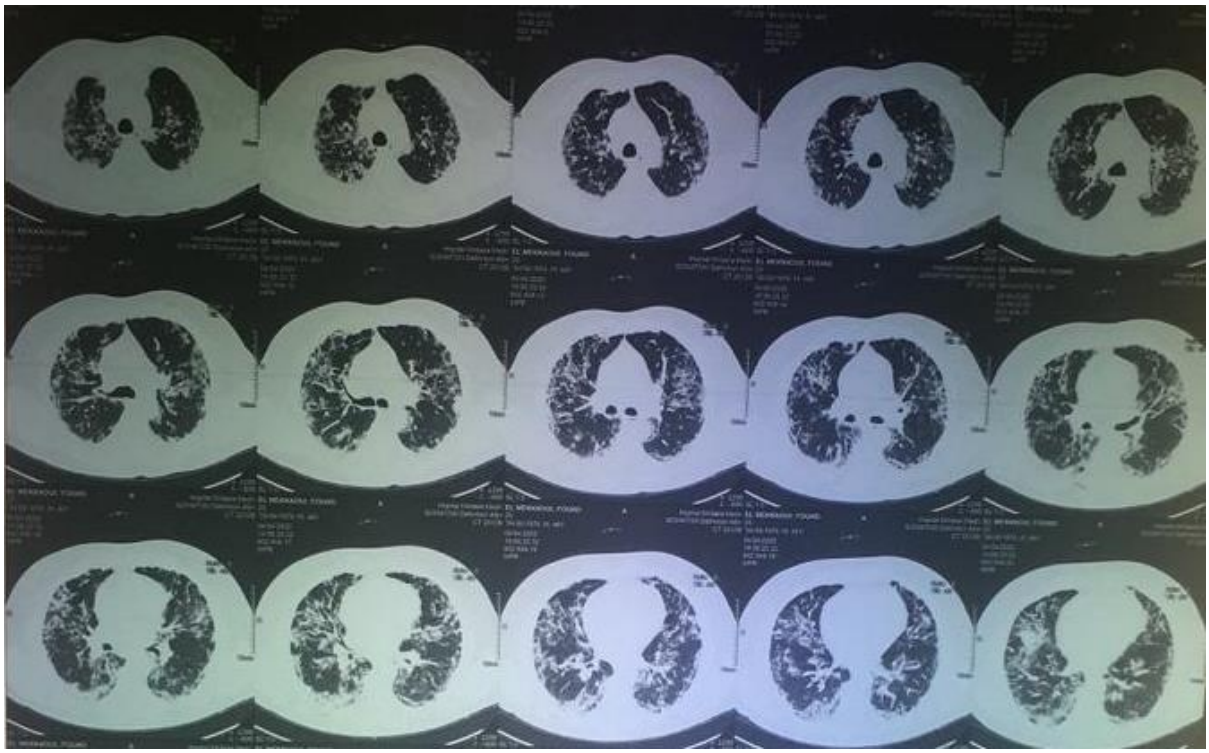


Figure 20: *Chest CT scan on admission of a 56 years old male patient M.F, that presented initially with fever, dry cough, headache and diarrhea, with underlying hypertension, diabetes and asthma.*

CT findings were listed CORADS 5, bilateral ground-glass opacities, associated with condensations and crazy-paving pattern, hitting all lobes, with an extent estimated at 25-50% (important extent), with also a mediastinal adenopathy, that represented a sign of severity.

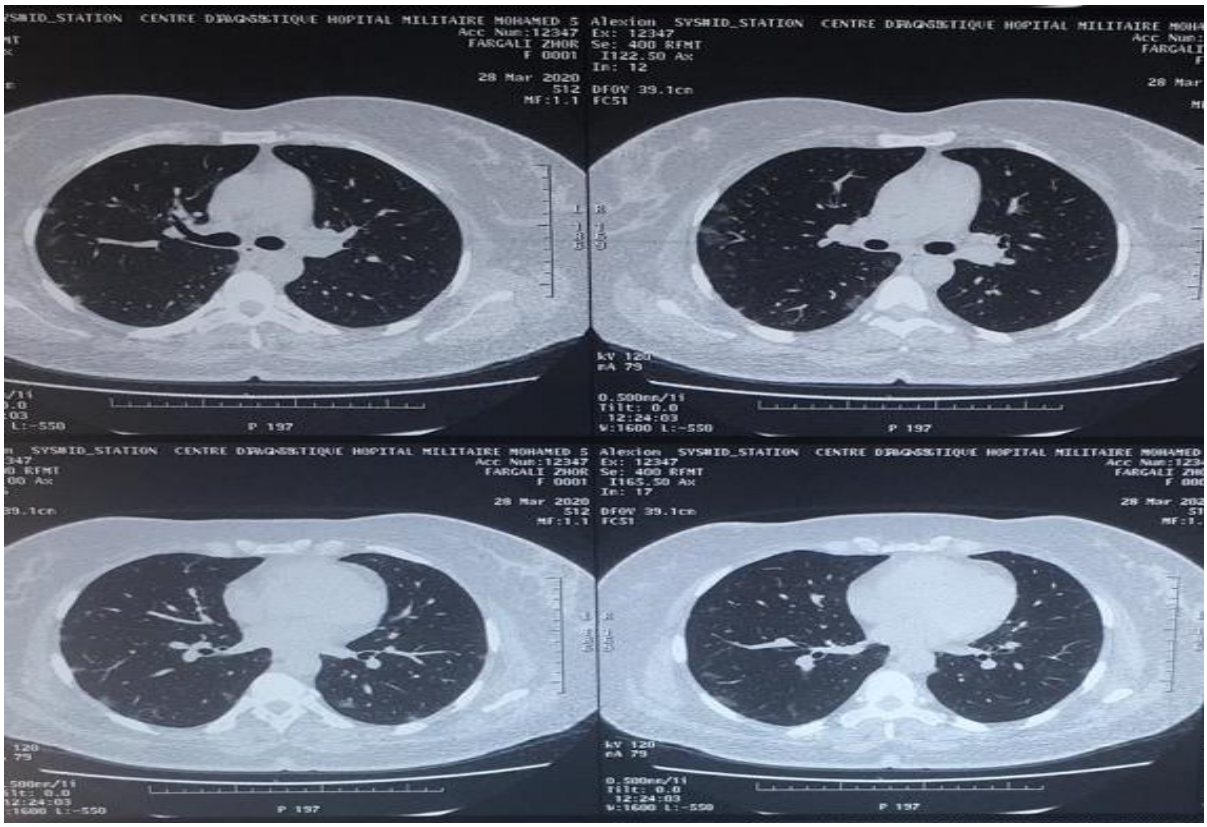


Figure 21: *Chest CT scan on admission of a 50 years old female patient F.Z, that presented initially with dry cough, arthromyalgia and headache, with no underlying comorbidities.*

CT findings were listed CORADS 5, bilateral ground-glass opacities, associated with condensations, hitting inferior lobes, with an extent estimated at 10-25% (moderate extent).

× *Indications as a diagnosis test*

CT (computed tomography) is particularly useful to help direct management in complex situations, in patients with clinical worsening, and for ruling out alternative diagnoses. The Sociedad Española de Radiología Médica [Spanish Association of Medical Radiology] (SERAM) has recommended to use CT scan in the following circumstances **[188]**:

- Clinical/analytical/radiological discordance: severely ill patients with high clinical or biological suspicion, a normal chest radiograph and difficulties getting PCR results, or negative or inconclusive PCR results.
- Patients with confirmed COVID-19 and clinical deteriorating and/or biological results suggestive of pulmonary embolism, or superinfection.
- Critically ill patients clinically suspected of having COVID-19 for whom a decision must be made regarding placement in a conventional (clean) ICU or an isolation ICU (for the COVID-19 patients).
- Patients with another serious disease, suspected or tentatively diagnosed with COVID-19, who require immediate treatment decisions and, so, prompt diagnosis in order to increase the protection of the concerned professionals (surgery, interventional techniques).

× ***CT findings in patients with COVID-19***

- ***Typical findings:***

- *Ground-glass opacities* (*Figure 22A*) **[189]**.
- *Consolidation* (*Figure 22B*) **[190]**.
- *Peripheral reticulation* (*Figure 22C*) **[190]**.
- *Crazy-paving pattern* (*Figure 22D*) **[189]**.

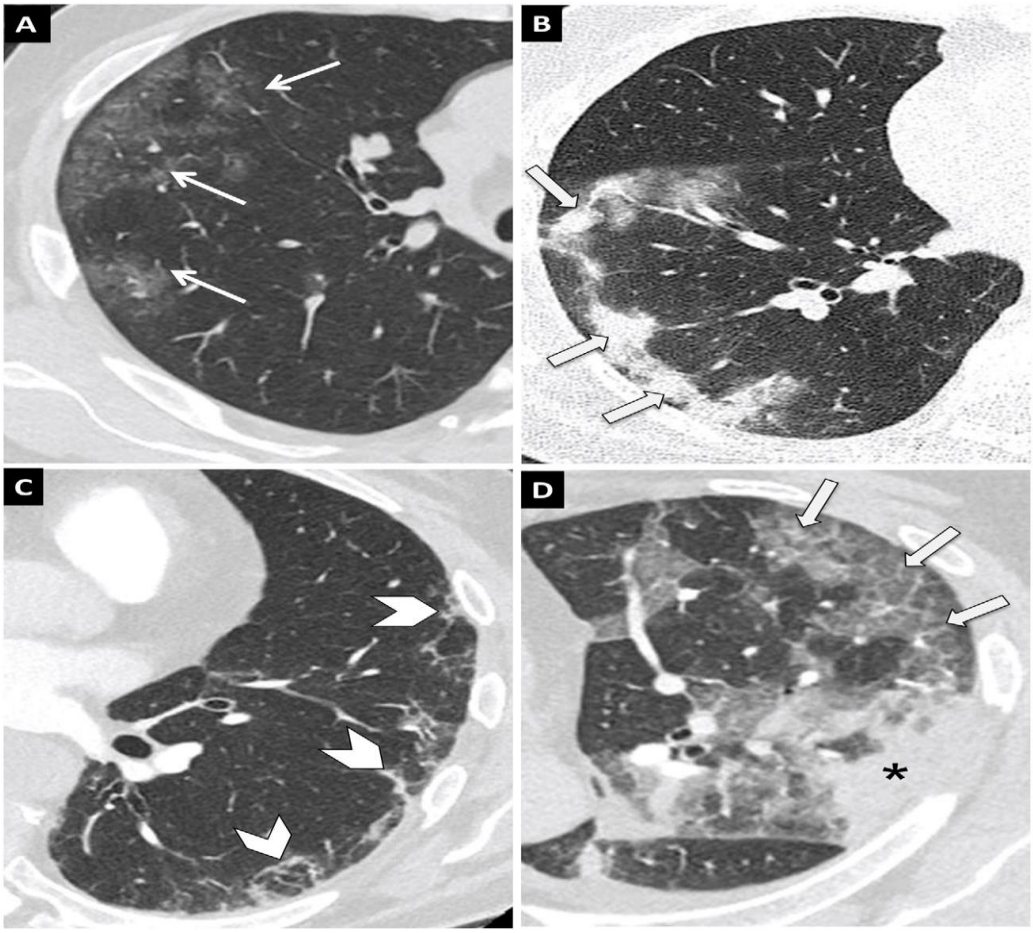


Figure 22: *Typical findings in COVID-19 pneumonia on computed tomography (CT). Axial chest CT images with 1-mm slice* **[134]**.

(A) Ground-glass opacities with rounded morphology and a peripheral and subpleural distribution (arrows).

(B) Consolidations with a peripheral and subpleural predominance (arrows).

(C) Reticulation with a peripheral and subpleural location (arrow tips).

(D) Peripheral ground-glass opacities with overlapping interlobular and intralobular septal thickening in relation to a crazy-paving pattern (arrow). Peripheral consolidation (asterisk) is also seen.

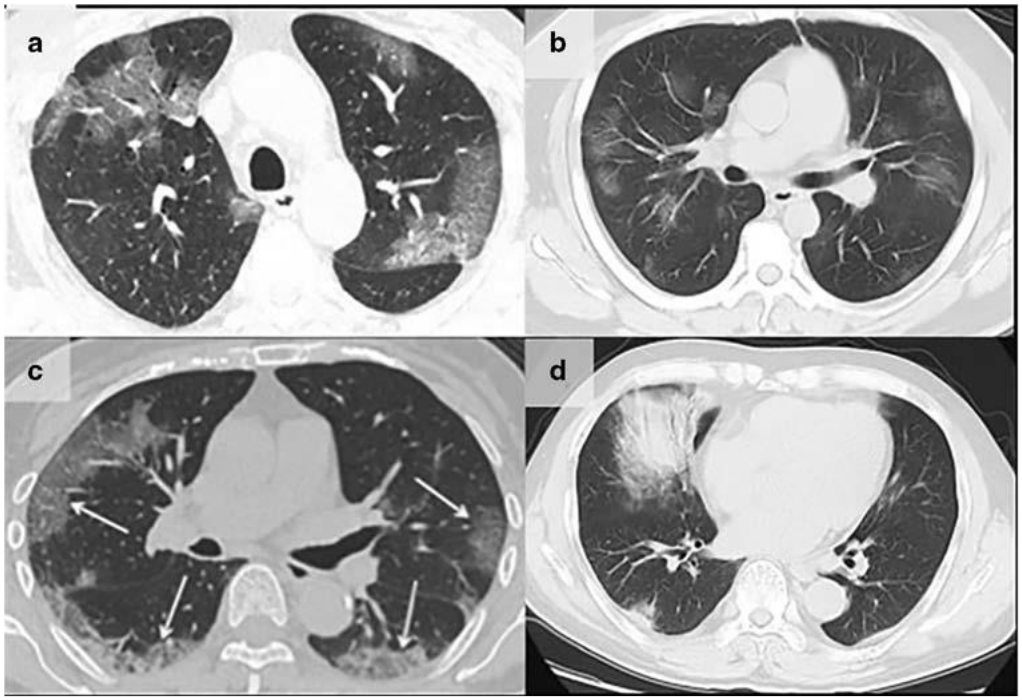


Figure 23: *Typical CT findings of COVID-19* **[1]**. Chest CT shows:

(a) multiple patchy areas of pure ground glass opacity (GGO) in a 75- year-old male and GGO with reticular and/or interlobular septal thickening.

(b) multiple patches, grid like lobule, and thickening of interlobular septa, typical "paving stone-like" signs in 38-year-old male chest CT image.

(c) bilateral ground glass and consolidative opacities with a striking peripheral distribution in an axial CT image obtained in 65-year-old female.

(d) large consolidation in the right middle lobe, patchy consolidation in the posterior and basal segment of right lower lobe, with air bronchogram inside in a CT image of a 65-year-old male.

- ***Other less common signs:***

- *Reversed-halo sign* (*Figure 24A and B*) **[142][189][191]**.
- *Air-bubble (vacuolar) sign* (*Figure 24C*) **[190]**.
- *Airway changes*.
- *Prominent vessels*: **[189]**.
- *Pleural and sub-pleural abnormalities*:
  - Pleural thickening associated with lung parenchyma abnormalities.
  - Sub-pleural curvilinear line (*Figure 25B*) **[192]**.

- Sub-pleural parenchymal band (*Figure 25C*).
- A hypoattenuating line between the visceral pleura and the lesion (*Figure 25D*) **[193][194]**.

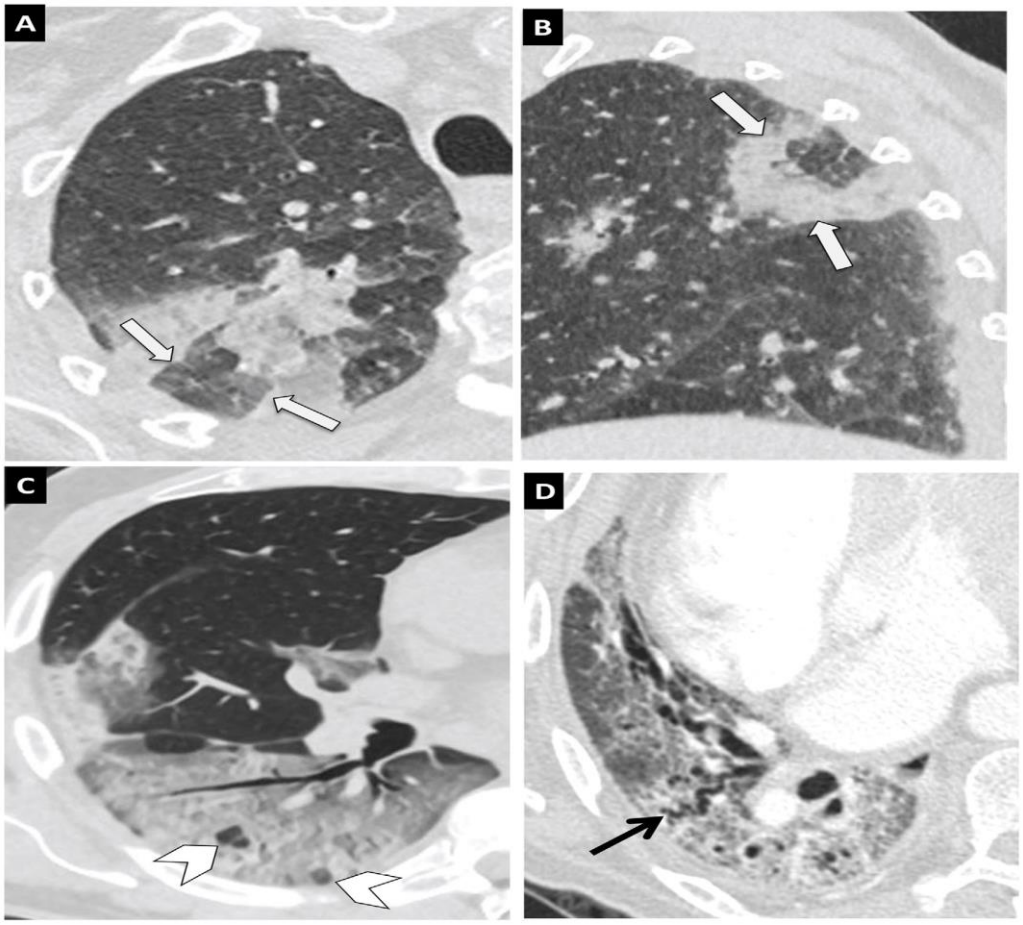


Figure 24: *Typical findings in COVID-19 pneumonia on computed tomography (CT). Images from a CT scan of the chest with 1-mm slices* **[134]**.

(A) Axial and **(B)** sagittal images showing a lesion in the posterior segment of the right upper lobe with the reversed-halo sign (arrows).

(C) Extensive ground-glass involvement with areas of consolidation in the right lower lobe with the vacuolar sign (arrow tips).

(D) Abnormal architecture of the right lower lobe with a crazy-paving pattern and bronchial dilation (black arrow).

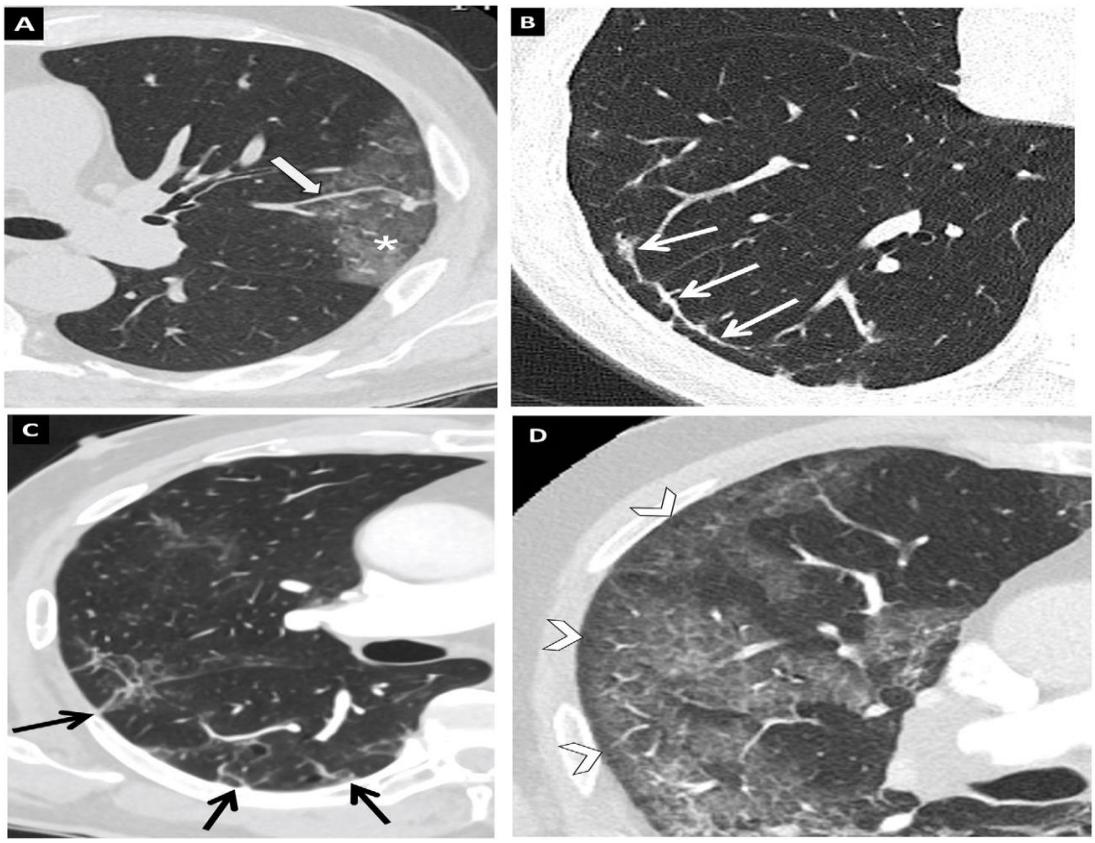


Figure 25: *Typical findings in COVID-19 pneumonia on computed tomography (CT). Axial chest CT images with 1-mm slices* **[134]**.

(A) Vascular thickening (arrow) associated with an area of ground-glass opacity (asterisk).

(B) Subpleural curvilinear line (arrow).

(C) Subpleural parenchymal bands (arrows).

(D) Hypoattenuating line (arrows) between visceral pleura and ground-glass opacity (arrow tips).

- ***Location and distribution***

The involvement is usually multifocal and bilateral, with a peripheral and subpleural distribution **[194]**. Unilateral ground-glass opacities may be present, mainly in the early stage of the disease **[195]**. Although all lung segments may be affected, there is a predilection for the lower lobes **[190]**.

- ***Indeterminate findings***

These are non-specific forms of presentation, as they can be found in both COVID-19 pneumonia, other pathogens induced pneumonia and even in non-infectious diseases.

These findings point to an alternative diagnosis **[193]**.

- *Non-peripheral patchy ground-glass consolidations or opacities*,
- *Ground-glass fibrosis*.
- *Pleural effusion*.
- *Lymphadenopathy*.

- ***Atypical findings***

- *Calcification*.
- *Cavitation*.
- Well-defined solid *nodules* or *masses*.
- *Focal consolidation*.
- *Bronchiolitis*.

- *Diffuse ground-glass opacities* with a *peri bronchovascular distribution*.
- *Fibrotic changes*.

× *CT findings according to the evolutionary stage of infection*

According to ***Pan** et al.*, some studies have reported pathological findings on pulmonary CT in asymptomatic patients **[195]**. There have also been reports of negative CT results during the first few days of symptoms. Therefore, negative CT results should not be used to rule out the possibility of COVID-19, particularly in early-stage disease. There is a link between radiological findings and time elapsed since the onset of symptoms **[191][196][197]** (*Figure 26*).

There is four evolutionary phases:

1. *Early phase (0-4 days after the onset of symptoms)*: the ground-glass pattern predominates, with unilateral or bilateral and multifocal involvement. It can show a rounded morphology. CT can also be normal (50% in the first two days).
2. *Progression phase (5-8 days)*: involvement with a ground-glass pattern progresses rapidly in extent and becomes bilateral and diffuse, with multilobar involvement. At this stage, areas of crazy-paving pattern and consolidations may appear **[193]**.
3. *Peak phase (9-13 days)*: maximum involvement is seen, with areas of ground-glass pattern transforming into consolidation. Consolidation is the predominant form of involvement. An air bronchogram, crazy-paving pattern and reversed-halo sign may be seen.

4. *<u>Resolution phase</u> (> 14 days)*: resorption of consolidations manifests again as ground-glass opacities that may be associated with bronchial dilations with subpleural distortion. Both subpleural parenchymal bands and subpleural curved lines may appear. The evolution of the lesions is often asynchronous, with certain areas showing resorption and others showing progression.

A Chinese study conducted by ***Shi** et al.*, including 81 patients with COVID-19 between December 20th 2019, and January 23d 2020, found that in some patients, interlobular and intralobular septal thickening associated with bronchial dilations gradually increases from the second week. These findings are indicative of interstitial disease, suggesting the development of fibrosis, although the course of the disease is not yet sufficiently understood to classify these changes as irreversible fibrosis **[193]**.

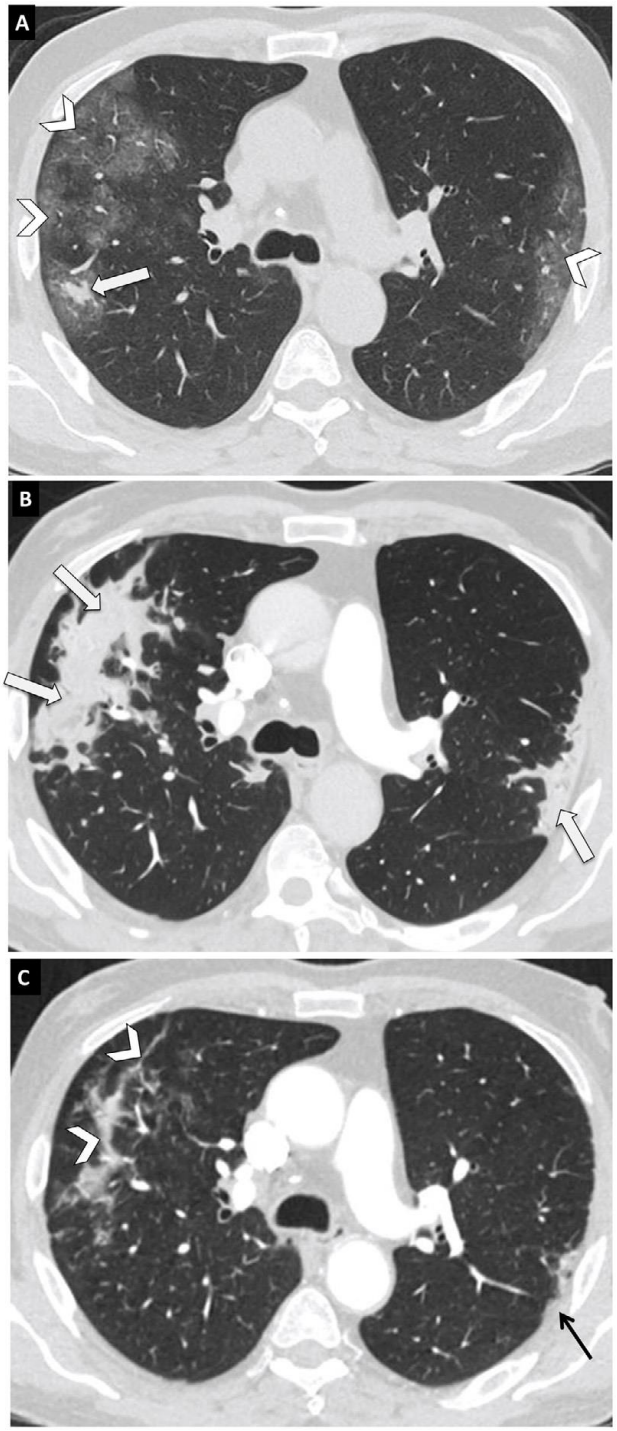


Figure 26: *Progression of COVID-19 pneumonia in a 56-year-oldwoman. Axial chest computed tomography (CT) images with a thickness of 1 mm at the level of the carina* **[134]**.

(A) Study 10 days after the onset of symptoms. Peripheral and bilateral ground-glass opacities (arrow tips) and a small consolidation forming in the posterior segment of the right upper lobe (arrow).

(B) CT scan 15 days after the first CT scan. Progression of ground-glass opacities to consolidations (arrows).

(C) CT scan 32 days after the first CT scan. Partial resorption of consolidations (arrow tips) and focal pleural thickening in the apico posterior segment of the left upper lobe (black arrow).

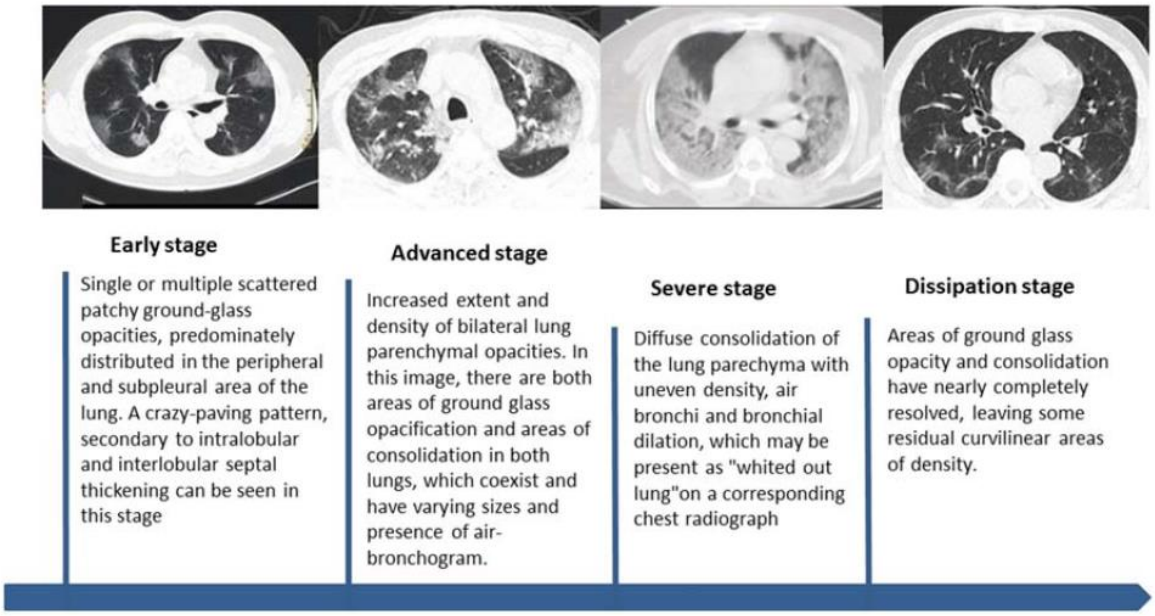


Figure 27: *CT manifestations of different stages of COVID-19* **[1]**.

× *Structured report*

A structured report allows a standardized language that can be understood by the entire medical staff. It must be correlated with the clinical suspicion, duration of symptoms and local prevalence. The Radiological Society of North America (RSNA) suggets four categories for COVID-19 pneumonia; typical, indeterminate, atypical and negative (*Table 13*) **[142]**. The Nederlandse Vereniging voor Radiologie [Dutch Association of Radiology] proposes a consensus for the structured reporting of findings on chest CT in patients with suspected COVID-19. This association developed the CO-RADS classification (COVID-19 Reporting and Data System), with a five-point scale for suspicion, from very low (CO-RADS 1) to very high (CO-RADS 5), for patients with moderate to severe symptoms in a setting of moderate to high prevalence (*Table 14*) **[198]**.

Table 13: *Classification system for findings of COVID-19 pneumonia on chest computed tomography (CT), a consensus endorsed by the American College of Radiology (ACR) and the Radiological Society of North America (RSNA)* **[142]**.

COVID-19 pneumonia imaging classification	CT Findings	Suggested reporting language
Typical appearance	Ground-glass opacities with or without consolidation or ''crazy-paving'' pattern Peripheral, bilateral, multilobar Reverse halo sign or other features of organising pneumonia	Fndings suggest COVID-19 pneumonia Differential diagnosis: other viral pneumonia (influenza), organising pneumonia, toxicity and connective tissue diseases
Indeterminate appearance	Absence of typical features and presence of: • Ground-glass opacities with or without consolidation and non-rounded or non-peripheral • Unilateral involvement • Few ground-glass opacities	Features can be seen in COVID-19 pneumonia, though they are non-specific and can occur with a variety of infectious and non-infectious processes.
Atypical appearance	Absence of typical or indeterminate features and presence of: • Lobar or segmental consolidations • Centrilobular or ''tree-in-bud'' nodules • Cavitation	Atypical features of COVID-19 pneumonia; consider alternative diagnosis
Negative findings	No CT features to suggest pneumonia	No CT features to suggest pneumonia

Table 14: *CO-RADS classification of the COVID working group of the Dutch Radiology Society: proposed standardized CT reporting system for patients with suspected COVID-19 in a setting of moderate to high prevalence* **[198]**.

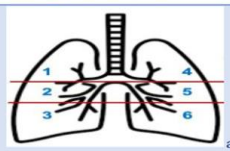
	Level of suspicion of COVID-19 infection	CT findings
CO-RADS 0	Not interpretable	Scan technically insufficient for assigning a score
CO-RADS 1	Very low	Normal or non-infectious disease (CHF, neoplasm, etc.)
CO-RADS 2	Low	Typical for other infection but not COVID-19 Example: typical bronchiolitis with tree-in-bud pattern, TB
CO-RADS 3	Indeterminate	Features compatible with COVID-19 but also other diseases Example: • Unifocal ground-glass opacity • Lobar pneumonia The diagnosis cannot be ruled out
CO- RADS 4	High	Suspicious for COVID-19 Examples: • Unilateral ground-glass opacity • Multifocal consolidations with no other typical findings • Findings suspicious for COVID-19 in underlying pulmonary disease
CO-RADS 5	Very high	Typical of COVID-19
CO-RADS 6	Proven	PCR positive for SARS-CoV-2

CHF: congestive heart failure; CT: computed tomography; PCR: polymerase chain reaction; TB: tuberculosis.

× *Severity and prognosis*

Most patients infected with SARS-CoV-2 have mild symptoms and a good prognosis. However, sometimes the virus may lead to severe disease in the form of pneumonia, pulmonary oedema, ARDS or multiple organ failure that can result in death. The study of clinical, biological and imaging factors associated with disease severity is the key to promoting effective treatment strategies that decrease complications and mortality. Chest CT is considered one of the main tools for assessing infection severity. It enables stratification of patients into risk categories with estimation of their prognosis, thus helping in clinical decision-making. The imaging finding most commonly associated with clinical severity is the extent of lung involvement. Multiple semi-quantitative scales have been proposed for CT that visually calculate the extent of the abnormalities (*Figure 13*).

Their disadvantage is their lack of accuracy. To overcome this shortcoming, artificial intelligence systems can perform a rigorous quantitative analysis of injured lung volume. Other lung abnormalities, that are significantly more common in patients with severe illness, include diffuse distribution of lesions, involvement of middle and central areas, consolidations, crazy paving pattern, interlobular septal thickening, bronchial wall thickening, air bronchogram, traction bronchiectasis, linear opacities, atelectasis and distorted lung architecture. Extra pulmonary lesions such as intrathoracic lymph node enlargement, and pleural and pericardial effusion, also seem to be associated with more severe disease (*Figure 28*) **[134]**.

<table>
<tr><th>Authors</th><th>Regions to be assessed</th><th>Scoring criteria</th></tr>
<tr><td>Xie et al.[62] y Zhao et al.[63]</td><td> 

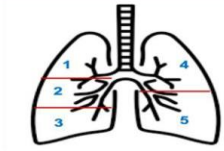
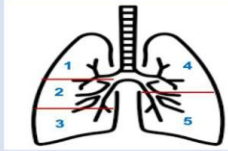
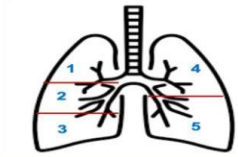
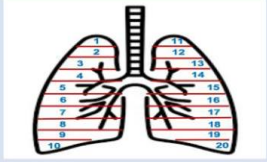
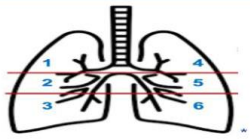
a</td><td>
<table>
<tr><th>Extent of damage for each area</th><th>Points</th></tr>
<tr><td>0%</td><td>0</td></tr>
<tr><td>< 25%</td><td>1</td></tr>
<tr><td>25-50%</td><td>2</td></tr>
<tr><td>50-75%</td><td>3</td></tr>
<tr><td>> 75%</td><td>4</td></tr>
</table>
</td><td>• Each of the 6 areas is given a score from 0 to 4
• The final score is the sum of the individual scores for each area and ranges from 0 to 24</td></tr>
<tr><td>Pan et al.[57] y Li et al.[60]</td><td> 
</td><td>
<table>
<tr><th>Extent of damage for each lobe</th><th>Points</th></tr>
<tr><td>0%</td><td>0</td></tr>
<tr><td>< 5%</td><td>1</td></tr>
<tr><td>5-25%</td><td>2</td></tr>
<tr><td>26-49%</td><td>3</td></tr>
<tr><td>50-75%</td><td>4</td></tr>
<tr><td>> 75%</td><td>5</td></tr>
</table>
</td><td>• Each of the 5 lobes is given a score from 0 to 5
• The final score is the sum of the individual scores for each lobe and ranges from 0 to 25b</td></tr>
<tr><td>Pan et al.[57]</td><td> 
</td><td>
<table>
<tr><th>No. of affected lobes</th><th>Points</th></tr>
<tr><td>1</td><td>1</td></tr>
<tr><td>2</td><td>2</td></tr>
<tr><td>3</td><td>3</td></tr>
<tr><td>4</td><td>4</td></tr>
<tr><td>5</td><td>5</td></tr>
</table>
</td><td>• The maximum score is 5</td></tr>
<tr><td>Chung et al.[67]</td><td> 
</td><td>
<table>
<tr><th>Extent of damage for each lobe</th><th>Points</th></tr>
<tr><td>0%</td><td>0</td></tr>
<tr><td>< 25%</td><td>1</td></tr>
<tr><td>25-50%</td><td>2</td></tr>
<tr><td>50-75%</td><td>3</td></tr>
<tr><td>> 75%</td><td>4</td></tr>
</table>
</td><td>• Each of the 5 lobes is given a score from 0 to 4
• The final score is the sum of the individual scores for each lobe and ranges from 0 to 20</td></tr>
<tr><td>Wu et al.[53] y Wan et al.[71]</td><td> 
</td><td>
<table>
<tr><th>No. of affected segments</th><th>Points</th></tr>
<tr><td>For each segment</td><td>1</td></tr>
</table>
<table>
<tr><th>Volume of involvement for each segment</th><th>Points</th></tr>
<tr><td>< 50%</td><td>0</td></tr>
<tr><td>≥ 50%</td><td>1</td></tr>
</table>
</td><td>PII = score by number of affected segments + score by volume of involvement for each segment/40 × 100[c]
• The results range from 0% to 100%, and higher values indicate a higher inflammatory load</td></tr>
<tr><td>Yuan et al.[70]</td><td> 
</td><td>
<table>
<tr><th>Extent of damage for each area</th><th>Points</th></tr>
<tr><td>0%</td><td>0</td></tr>
<tr><td>< 5%</td><td>1</td></tr>
<tr><td>5-25%</td><td>2</td></tr>
<tr><td>26-49%</td><td>3</td></tr>
<tr><td>50-75%</td><td>4</td></tr>
<tr><td>> 75%</td><td>5</td></tr>
</table>
<table>
<tr><th>Attenuation of damage for each area</th><th>Points</th></tr>
<tr><td>Normal attenuation</td><td>1</td></tr>
<tr><td>Ground-glass opacities</td><td>2</td></tr>
<tr><td>Consolidation</td><td>3</td></tr>
</table>
</td><td>•The maximum score is 72[d]</td></tr>
</table>

Figure 28: *Semi-quantitative scales to assess the extent of lung lesions due to COVID-19 pneumonia with computed tomography* **[134]**.

[a] Upper regions (1 and 4) above carina; middle regions (2 and 5) between carina and inferior pulmonary vein; lower regions (3 and 6) below inferior pulmonary vein.

[b] ***Li*** *et al.* **[199]** showed that the classification with a cut-off point of 7 had a sensitivity of 80% and a specificity of 82.8% for distinguishing between severely and mildly ill patients (area under the curve [AUC] 0.87).

× *Clinical correlation and pathology findings on CT scan*

The ‘‘Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection by the [Chinese] National Health Commission (Trial Version 5)’’ clinically identifies four levels of severity **[200]**:

1. *Mild:* Patients with mild symptoms and no abnormalities on CT. The virus is located in the upper respiratory tract and has not progressed to the alveoli, so there is no pulmonary reaction.
2. *Common:* Patients with fever or respiratory infection signs, and pneumonia changes on CT scan.

   They usually present areas of ground-glass attenuation representing partial occupation of the alveolar spaces by exudate. The alveolar wall is intact.
3. *Severe:* Patients meeting at least one of the following criteria:

   - Respiratory distress, respiratory rate ≥ 30/min.
   - Finger oxygen saturation (SaO2) 93% at rest.
   - Partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) 300 mmHg **[134]**.

   CT may show a crazy-paving pattern. According to ***Wang*** *et al.*, 70% of patients with this abnormality will be classified as severely or critically ill. It is caused by an alveolar pattern as well as an interstitial pattern. It reflects an increase in alveolar exudate and dilation with increased permeability of the capillaries of the interlobular septa, causing interlobular interstitial edema **[201]**.

4. *Critical:* Patients with at least one of the following criteria:

   - Respiratory failure requiring mechanical ventilation.
   - Shock condition.
   - Multiple organ failure.

   On the CT scan, they show extensive diffuse consolidations that may have a "white-out" appearance. They are due to an alveolar injury with accumulation of exudates and edema in the alveolar cavity, resulting in a ventilation-perfusion defect. This, together with an abnormal immune reaction (immune dysregulation), eventually leads to ARDS and a severe systemic clinical picture **[134]**.

Finally, imaging tests play a major role in the management of patients with suspected or confirmed COVID-19. The initial imaging test is the chest X-ray. CT scan, which is more sensitive, is reserved for detecting possible complications and providing alternative diagnoses, in the cases of clinical, biological and radiological discordance, or when microbiological diagnosis is not possible **[134]**.

However, early in the disease, chest computed tomographic imaging findings in approximately 15%, and chest radiography findings in approximately 40% of individuals can be normal, which cannot rule out the infection **[164]**.

COVID-19 pneumonia is characterized by the presence of ground-glass opacities and/or consolidations, which are typically bilateral and peripheral, often sub-pleural and more frequently in the lower fields.

Regarding clinical course, reparative changes appear as early as the second week of the disease, characterized by sub-pleural lines, greater sub-pleural distortion and bronchial dilations. In addition, imaging tests are used to monitor the course of the disease, and to assess of the severity of lung involvement **[134]**.

5. PCR or CT scan?

According to current diagnostic criteria, identification of the viral pathogen via nucleic acid detection (usually from swab test) is considered as the gold standard and formative assessment for the diagnosis of COVID-19. However, due to various problems of virus detection in the clinical setting such as irregular sampling of samples, laboratory error, insufficient viral material in the specimen, improper extraction of nucleic acid from clinical materials, and contaminatory and technical problems, there have been false negatives, which makes imaging examination an indispensable mean not only in the early detection and diagnosis, but also in monitoring the clinical course, evaluating the disease severity, and may be presented as an important warning signal preceding the negative RT-PCR test results. Additionally, chest CT showed progression of disease that corresponded with worsening clinical symptoms, and also disease resolution as the patients clinically recovered **[1]**.

According to ***Majidi*** *et al.*, some studies have reported that chest CT images have the sensitivity of 80–90% and specificity of 82.8–96% for detecting the lung lesions in patients with COVID-19 **[202]**.

A Chinese study conducted by ***Long*** *et al.*, from January 20th to February 8th, 2020, included a total of 36 cases diagnosed with COVID-19 pneumonia. 35 patients had abnormal CT findings at presentation, and only one patient had a normal chest CT. Using RT-PCR, 30 cases showed positivity, with 6 cases

initially missed. Amongst these 6 missed cases, 3 had a positive result in the second RT-PCR test (after 2 days, 2 days and 3 days respectively), and the other 3 were positive in the third round of RT-PCR assessments (after 5 days, 6 days and 8 days respectively). Therefore, sensitivity of CT examinations was 97.2% at presentation, whereas first round RT-PCR sensitivity was 84.6% **[203]**.

Ultimately, CT examinations appear sensitive to virus detection, whereas RT-PCR may produce false- negative results. We therefore recommend that patients with positive imaging findings but negative RT-PCR results should be isolated and RT-PCR repeated to avoid misdiagnosis **[203]**.

6. Serology

In our study, serology was not performed for diagnosis purposes, but in order to establish the evolution of the serological and immunological profile of patients. So, the relative data was not included in our results.

Serological changes have important significance in the diagnosis of COVID-19. Detection of IgM and IgG antibodies may predict the burden of the viral infection. However, since IgM responses are nonspecific **[161]** and they are detectable within 5 days of infection, with a higher-level during weeks 2 to 3 of illness **[11]**, and the development of IgG occurs over a few weeks **[161]**, with a first response seen approximately 14 days after symptom onset, serological assays may be not applicable for acute infections, but for advanced cases **[204]**.

Additionally, a Chinese study conducted by ***Zhang*** *et al* between January 25 and March 18, 2020, enrolled 21 patients including 11 (52.4%) non-severe COVID-19 patients, 5 (20.8%) severe patients, and 5 (20.8%) asymptomatic cases with SARS-CoV-2 infection, and reported that the seropositive rate increases with the

duration of the disease in symptomatic cases, and seroconversion occurs early in severe cases, while specific antibody responses are generated at later stages in asymptomatic cases, with a lower antibody titer than symptomatic patients. Besides, the symptomatic cases have heavy viral burden than asymptomatic cases. It is probably because the body immune response intensity is partially dependent on the number of viruses **[205]**.

Hence, serological characteristics can be used to distinguish the severity of the disease **[161]**.

However, test performance, accuracy, and validity are variable **[206]**.

A Moroccan study was published on July 2021, conducted by ***Tagajdid*** *et al.*, and aimed to evaluate the sensitivity of nine SARS-CoV-2 antibodies immunoassays. 80 blood samples were collected from PCR-confirmed COVID-19 patients in the Laboratory of Virology, Center for Virology, Infectious and Tropical Diseases, (20 samples collected at day 10 after the onset of symptoms, 60 collected after day 14 following the onset of symptoms) and 20 blood samples from patients SARS-CoV-2 RT-PCR negative. The results concerning the most commonly used assay found a sensitivity of 38.24% (22.17–56.44) at day 10, and 98.44% (91.60–99.96) after the 14^{th} day **[207]**.

On a report published on April 2020 in Australia, by ***Bond*** *et al,* aiming to evaluate three serological assays for COVID-19, the sensitivity for detecting IgM or IgG was 52.4% to 57.1% between 9^{th} and 14^{th} day and 77.8% to 88.9% between the 21^{st} and 30^{th} day **[206]**.

Thus, it occurs that as the duration of symptoms increases, so does the sensitivity.

D. Differential diagnosis

Differential diagnosis of typical COVID-19 symptoms is very broad and comprises many common respiratory, infectious, and cardiovascular diseases, whereas respiratory diseases are the most frequent. Older patients may be even more challenging since the clinical picture may be atypical with syncope and malaise **[208]**.

Patients with COVID-19 present with similar symptoms as COVID-19 negative respiratory infections, so clinical discrimination is not reliable. According to ***Fistera*** *et al.*, in their study including 314 patients presenting with conceivable COVID-19 symptoms between March and April, 2020, dyspnea was less frequently found, whereas dysgeusia was significantly more prevalent **[209]**. Whenever present, dysgeusia should raise high suspicion for COVID-19, especially during a pandemic. Dyspnea is a typical symptom of COVID-19, which could be found in about 29% of cases in a study of 270,000 patients in the U.S. **[168]**. Controversially, several authors described a specific phenomenon called “happy hypoxemia” in COVID-19 with a disconnect between the severity of hypoxemia and relatively mild respiratory discomfort **[210][211]**.

The CT appearance of COVID-19 shares some similarities with other diseases that cause viral pneumonia, including influenza viruses, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, etc. In particular, those within the same viridae (SARS and MERS) have great similarities in imaging findings because they belong to the same Coronaviridae family, and thus need to be excluded through clinical manifestations and laboratory pathogen detection **[1]**. Imaging in MERS pneumonia can also show ground glass lesions in the sub-pleural and basal parts with consolidation, and

fibrosis changes can be left after healing. In the pneumonia patients infected by respiratory syncytial virus, chest CT mainly manifested as small centri-lobular nodules and areas of consolidation which are often asymmetrically distributed in the lungs. Adenovirus pneumonia shows bilateral multifocal ground glass opacities with patchy consolidations on CT images and may show lobar or segmental distribution. Human parainfluenza virus pneumonia may show centri-lobular nodules with bronchial wall thickening that differentiates it from the imaging appearances of the other viruses. Radiographs in patients with influenza pneumonia show bilateral patchy areas of ground glass opacity with or without focal areas of consolidation, usually in the lower lobes **[212]**. In a report on H1N1 influenza infection, in addition to the most common findings of ground glass opacity, interlobular septal thickening, and centri-lobular nodules were the second most frequent findings **[213]**. Rapidly progressive ground glass opacities and consolidations with air bronchograms and interlobular septal thickening, with right lower lobe predominance, are the main imaging findings in H7N9 pneumonia **[214]**. Viruses are a common cause of respiratory infection and recognition of viral pneumonia patterns may help in the differentiation among viral pathogens, while the definite diagnosis is achieved by laboratory detection of virus. In addition, COVID-19 also needs to be distinguished from mycoplasma pneumonia, chlamydia pneumonia, and bacterial pneumonia. Other diseases that need to be identified are vasculitis, acute interstitial pneumonia, connective tissue-related lung disease, and cryptogenic organizing pneumonia **[1]**.

V. TREATMENT

In our study, all patients benefitted from the national protocol, which was initially based on the combination of Hydroxychloroquine and Azithromycin (Appendix *Figure 4*).

This protocol has been updated according to the evolution of scientific data.

Currently, we know that the disease evolves in 2 phases **[215]**.

After an incubation of approximately five days, 70% of infected patients develop cough, fever, or dyspnea **[164]**.

This phase of viral invasion is followed, in some patients, by an inappropriate immune response, characterized by the worsening of the respiratory symptoms, and the inflammatory syndrome, usually eight to ten days after the first symptoms **[183]**. This dysimmune phase, sometimes called cytokine storm, may be associated with coagulopathy, which, for some authors, corresponds to viral sepsis **[216]**.

If the patient is in the first pulmonary phase, the treatment is based on the combination of Hydroxychloroquine and Azithromycin.

And if signs of distress and/or inflammatory syndrome, it is rather the announcement of the cytokine storm, and the treatment is then centered on corticosteroids, antibiotic therapy, tocilizumab **[112][161]** (Appendix *Figure 5*).

This protocol was associated to supportive care, such as oxygen therapy, vitamin therapy, with potentially adding antibiotic therapy (based on beta-lactam; either amoxicillin or 3d generation cephalosporins) and/or antiviral treatment (based on lopinavir/ritonavir) when needed; i.e. noticing clinical and/or biological signs suggesting a superinfection or progression, and adding anticoagulant treatment based on low molecular weight heparin (LMWH) in case of biological coagulation disorder (elevated d-dimer) alongside with lung lesions in CT Scan.

A. Current COVID-19 treatment options

For the management of COVID-19, there is a need to strengthen supportive care and closely monitor the vital signs, laboratory examination results and imaging findings of the patients. Providing effective oxygen therapy on time is also essential **[161]**.

Antiviral agents or the modulators of the immune function are some of the proposed options. Lopinavir/ritonavir, hydroxychloroquine/chloroquine, remdesivir, ivermectin, favipiravir, umifenovir, camostat, nitazoxanide, minocycline, corticosteroids, tocilizumab, sarilumab, siltuximab, anakinra, interferons (IFN), adalimumab, and baricitinib/ruxolitinib have been studied, with conflicting results **[217]**.

Furthermore, adverse reactions of the above drugs, contraindications, and interactions with other drugs should be closely monitored. Uninformed or inappropriate use of antibiotics, especially a combined use of broad-spectrum antibiotics, should be avoided.

For severe cases or critically ill patients, on the basis of symptomatic treatment, secondary infections and complications should be actively prevented or treated, any underlying diseases treated, and timely organ function support should be provided **[161]**.

Numerous studies and clinical trials are underway to develop effective treatment options for COVID-19. Corticosteroids can suppress lung inflammation; hence they have been used to treat SARS and MERS. However, they may also inhibit the immune response of the patient, thereby slowing the elimination of pathogens. In addition, available observational data indicate that corticosteroids

can increase mortality and secondary infection rates when treating infections caused by influenza, SARS and MERS viruses **[218]**. Therefore, corticosteroids should be used with caution. The World Health Organization (WHO) guidelines for clinical care released on January 28, clearly state that routine use of systemic corticosteroids to treat viral pneumonia or acute respiratory distress syndrome is not recommended, unless supported by a specific reason **[219]**.

B. Protocol associating Hydroxychloroquine with Azithromycin

Hydroxychloroquine and chloroquine are medications that have been used for a long time. Their most common use is for the treatment and prophylaxis of malaria. However, these antimalarial drugs are known to also have anti-inflammatory and antiviral effects, and are used for several chronic diseases such as systemic lupus erythematosus with low adverse effects.

The antiviral action of hydroxychloroquine and chloroquine has been a point of interest to different researchers due to its mechanism of action. Several in vitro studies have proven their effectiveness on severe acute respiratory syndrome virus and currently both in vitro and in vivo studies have been conducted on COVID-19. The effect of hydroxychloroquine and chloroquine on viral replication goes beyond cytokine inhibition. These medications are weak bases that can affect acid vesicles and inhibit several enzymes. This characteristic allows them to inhibit the viral entry to the cell when the endocytosis is pH dependent. It also inhibits glycosyl-transferases, viral post-translational modifications and replication of some viral families. The antiretroviral effect has been considered to be caused by the inhibition of viral glycosylation, a major antiviral mechanism of these drugs. It was also recently described that chloroquine might inhibit quinone reductase-2, an enzyme involved in sialic

acid biosynthesis. If this were to be true, it would explain further its effect on HIV, SARS and orthomyxoviruses because sialic acid is present on HIV-1 glycoproteins, SARS angiotensin-converting enzyme 2 (ACE2 receptor and orthomyxovirus receptors) **[220]**.

Azithromycin is an antibiotic that belongs to the macrolide family used in a wide variety of bacterial diseases. Beyond its antibacterial activity, this macrolide has shown antiviral and immunomodulatory activities that could be of interest in viral infections, including COVID-19.

Azithromycin could act on SARS-CoV-2 binding to respiratory cells. Its intracellular accumulation led to an increase in the pH that may impair trans-Golgi network (TGN) and lysosome functions. Using molecular dynamic simulations, another direct antiviral mechanism of this macrolide was theorized. Azithromycin resulted in a ganglioside-mimic given its similar volume and analogous chemical features than GM1. Since the spike protein of SARS-CoV-2 displays a ganglioside-binding site, azithromycin might inhibit SARS-CoV-2 infection by binding to this site. This would prevent the virus spike protein to reach gangliosides on the host plasma membrane, which is involved in SARS-CoV-2 pathogenesis. In addition, azithromycin may interfere in the spike protein/CD147 interaction or CD147 expression. The increase in the lysosomal pH by azithromycin may also alter the endocytosis process and lysosomal proteases function (cathepsins or furins), which may difficult the fusion process. As with other therapies, the use of azithromycin in the treatment of COVID-19 is a matter of debate. This drug presents promising pharmacokinetic and pharmacological characteristics that could be useful in the treatment of SARS-CoV-2 infection **[217]**.

In a French study conducted by ***Gautret** et al.*, in a cohort of 80 relatively mildly infected patients treated with a combination of hydroxychloroquine and azithromycin over a period of at least three days, with three main measurements: clinical outcome, contagiousness as assessed by PCR and culture, and length of stay in infectious disease unit (IDU), all patients improved clinically except two patients. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. Consequently, patients were able to be rapidly discharged from IDU with a mean length of stay of five days.

Thus, this study provided evidence of a beneficial effect of co-administration of hydroxychloroquine with azithromycin in the treatment of COVID-19 and its potential effectiveness in the early reduction of contagiousness. Given the urgent therapeutic need to manage this disease with effective and safe drugs, and the negligible cost of both hydroxychloroquine and azithromycin, there is an urgent need to evaluate this strategy further, both to treat and cure patients at an early stage before irreversible severe respiratory complications take hold, and to decrease duration of carriage and avoid the spread of the disease **[221]**.

However, ***Ennibi** et al*. conducted a prospective descriptive analytical study at the Center for Virology, Infectious and Tropical Diseases in Morocco, including 125 patients between March and May 2020, to assess the efficacy of hydroxychloroquine associated with azithromycin for the treatment of patients with COVID-19, based on viral clearance.

121 patients (96.8%) were cured after 10 days of treatment, and 32 patients (25.6%) had an early viral clearance on the 6^{th} and 8^{th} day respectively.

Although clinical healing was achieved in the majority of patients, the early viral clearance was obtained in only 25.6% of the patients, which is inconsistent with work published by other teams regarding early viral clearance in patients who received the same treatment protocol **[222]**.

Furthermore, ***Lamback*** *et al.* conducted a retrospective comparative study in Brazil, from March through June 2020, involving 193 adult patients hospitalized for mild and moderate COVID-19 related ARDS, analyzing treatment efficacy based on clinical and biochemical outcomes.

The active group comprised 101 (52.3%) patients using hydroxychloroquine associated with azithromycin and the control group 92 (47.7%) patients who did not take these medications.

In the medication group, 25% (25 out of 101) were admitted to the ICU, compared to 21% (19 out of 92) in the control group ($p > 0.05$). No difference in mortality, duration of non-invasive oxygen use or duration of hospitalization was seen between groups. The therapeutic regimen was well tolerated, with only 8 (7.9%) patients presenting gastrointestinal symptoms and 8 (7.9%) patients withdrawn treatment due to QTc prolongation.

Thus, patients treated with hydroxychloroquine combined with azithromycin and the control group had similar clinical outcomes. This therapeutic regimen was considered ineffective in hospitalized patients with mild to moderate COVID-19 related ARDS and was associated with few non-severe adverse events **[223]**.

C. Oxygen therapy

Administration of timely and effective oxygen therapy to patients with COVID-19 is recommended. If possible, the patients should be treated with mixed inhalation of hydrogen and oxygen (H2/O2: 66.6/33.3%). Patients with severe cases of COVID-19 rapidly progressed to ARDS, causing multiple organ failures and even death. Therefore, respiratory symptoms need to be treated urgently. For example, ***Zhan*** *et al* reported that extracorporeal membrane oxygenation (ECMO) technology was successfully used to treat a patient with COVID-19. This suggests that early application of ECMO can effectively reduce the deterioration and enhance recovery of the disease **[224]**.

Another study reported that the drugs acetazolamide, nifedipine and phosphordiesterase inhibitors can also be used to adjunctively treat COVID-19, thus improving lung ventilation conditions **[225]**.

D. Immunotherapy

Zhou *et al* reported a clear trend of IgG and IgM titer increase by monitoring the serum viral antibody levels in infected patients. The IgG-positive samples could neutralize the virus to some extent **[23]**. According to research by experts, most patients with new coronavirus infections will consistently produce new coronavirus-specific antibodies after treatment and rehabilitation, and these specific antibodies can effectively kill and eliminate the virus. On February 8th, 2020, the plasma antibodies from convalescent patients were used to treat patients for the first time at the First People's Hospital of Jiangxia District/Concord Jiangnan Hospital. Nine critically ill patients in this hospital received the treatment, and three serum samples were provided to critically ill patients in other hospitals. Based on the condition of severely ill patients in this

hospital, after 12 to 24h of treatment, blood oxygen saturation and the proportion of lymphocytes increased, the main inflammatory indicators decreased significantly, and the clinical symptoms began to improve comprehensively **[226]**.

An envelope-anchored spike protein (S protein) mediates coronavirus entry into host cells by first binding to a host receptor and then fusing viral and host membranes. During entry, the virus binds to a receptor on the surface of host cells. The receptor is known as ACE2. In addition, work carried out by ***Yi*** and his team at Wuhan Institute of Viruses, shows that SARS-CoV-2, similar to SARS-CoV, enters cells through ACE2, suggesting that drugs targeting ACE2 and SARS drugs may be used to treat COVID-19, which is worthy of further research **[227]**.

A number of related drugs are also being tested in clinical trials **[23]**.

The RNA of the SARS-CoV-2 sits at the core, surrounded by nucleocapsid proteins, which are coated with spike proteins, envelope proteins and membrane proteins. In addition to these proteins that maintain the structure of the virus, viral RNA can also direct the production of other viral proteins (present in infected cells and not in viral particles) that are not involved in the structure of the virus. These proteins are foreign to the host, and the body produces antibodies against them. As a result, though individuals infected with SARS-CoV-2 can produce a wide variety of antibodies against the virus, only antibodies that recognize the proteins on the surface of the virus particles might have an antiviral effect. Antibodies against S protein, known as neutralizing antibodies, bind to S protein and block its binding to ACE2, thus protecting host cells. In addition, non-neutralizing antibodies bind to the virus through its

variable region, while the constant region binds to the phagocytes, thus greatly facilitating phagocytes to clear the virus. However, this pattern can lead to the overactivation of non-specific immune cells, releasing large amounts of pro-inflammatory factors, typically IL-1, IL-6 and tumor necrosis factor (TNF), forming so-called cytokine storms, which are an important cause of ARDS and multiple organ dysfunction syndrome. Moreover, neutralizing antibodies are powerless against viruses that have already entered the host cells. They can only prevent most of the virus from entering the host cells; however, a small part of the virus can still enter the host cells. For viruses that enter the cells, their death depends on T cells in the body. Viruses that invade cells express information about their encoded proteins on the surface of the infected cell, and T cells recognize this information to attack the infected cell and ultimately kill both the infected cells and the viruses inside. In addition, since the plasma of the donor is an alien component to the patients, it is likely to cause an allergic reaction or infection caused by blood transfusion, such as acquired immune deficiency syndrome (AIDS) and syphilis. Therefore, plasma therapy is risky and suitable for critically ill patients with low immunity and without a cytokine storm, and is not recommended for patients with mild cases. Finally, plasma therapy must be used with caution, and should be further studied **[161]**.

Monoclonal antibodies (MAs) are generally regarded as effective and therapeutically specific towards viral infections because they prevent the virus from entering the host cells through binding with the S protein or ACE2 receptor. While MAs are highly effective, their rapid mass production is unrealistic and therefore unlikely to be appropriate for this burgeoning pandemic **[228]**.

Currently, Chinese treatment guidelines list interferon as an alternative agent for treatment. Some other immunomodulatory agents, such as baricitinib, imatinib, dasatinib and cyclosporine might work towards inhibiting SARS-CoV-2 **[229]**.

E. Virus blocking and pathway inhibitors

At present, targeting the renin-angiotensin system (RAS) is an important approach for the treatment of pulmonary diseases. ACE/AngII/AT1R is an important factor in promoting acute lung injury, which can be alleviated by the antagonistic role played by ACE2/Ang (1-7)/Mas receptor pathway. Therefore, it is predicted that the combination of SARS-CoV-2 and ACE2 would inhibit the ACE2/Ang (1-7)/Mas receptor pathway and decrease the ratio of ACE2/ACE, particularly in the elderly patients. However, the activity of ACE/AngII/AT1R pathway increased, thus leading to an unbalanced RAS. Then the increased inflammatory factors would increase mortality rate. Thus, activation of the ACE2/Ang (1-7)/Mas signaling pathway or inhibition of the ACE/Ang II/AT1R pathway may be an important therapeutic choice for COVID-19. In light of this fact, two ACE2 activators, resorcinol-naphthalein and 1-[(2-dimethylamino) ethylamino]- 4- (hydroxymethyl)- 7- [(4-methylphenyl)sulfonyloxy] -9H-xanthene-9-1 can be alternative therapies for COVID-19 **[230]**. Under controlled blood pressure, the application of ACE inhibitors (ACEI) and AT1R inhibitors in COVID-19 patients may reduce pulmonary inflammation and mortality **[231]**.

In addition, it is reported that APN01, a soluble recombinant human ACE2 (rhACE2), can block virus cell entry by competitively intercepting the SARS-CoV-2. There are some predictive drugs that can prevent the virus from invading, such as camostat, nafamostat, bromhexine, aprotinin, chlorpromazine, baricitinib, and ruxolitinib.

However, these drugs need more clinical trials to test their efficacy and safety. In case of cellular signaling pathway inhibitors, the potent protein kinase B (PKB, Akt) inhibitors MK-2206, niclosamide, diltiazem, nitazoxanide, tizoxanide and valinomycin, and the inhibitors of ERK/MAPK and PI3K/AKT/mTOR signaling pathways such as sirolimus, everolimus and metformin are being studied in clinical trials to verify their effectiveness **[23]**.

F. Suppression of cytokine storms and bacterial infections

Zhang *et al* proposed a treatment program that shortened the course of the disease in critically ill patients. The study reported that cytokine storms were found in critically ill patients. Through the artificial liver blood purification technology, inflammatory factors were removed and cytokine storms were eliminated, resulting in improved patient symptoms of breathing difficulties and blood oxygen saturation **[232]**. The intestinal microecology of these patients is often disordered; therefore, a treatment method should be adopted to ensure microecological balance and to provide enteral nutrition, supplement microecological regulators, to reduce secondary infection caused by bacterial transfer **[161]**.

At the same time, a study conducted by ***Yang*** *et al*. stressed on the blood purification treatment for patients with severe COVID-19. Immune damage mediated by cytokine storms and concomitant acute kidney injury (AKI) is a key factor for poor prognosis **[233]**. Therefore, blood purification is urgently needed in critical cases, and its application should follow the detailed principles and protocol involved. The blood purification techniques include continuous renal replacement therapy (CRRT), blood/plasma perfusion, absorption, plasma replacement, and other modes of comprehensive blood purification **[234]**.

In addition, there are also other ways to suppress cytokine storms, such as non-steroidal anti-inflammatory medication, immunosuppressants, IFN-λ, corticosteroids, cytokine antagonists, blockers and inhibitors, intravenous immunoglobulin (IVIg), mesenchymal stem cells, sphingosine-1-phosphate receptor 1 agonists, and enabling an increase in vascular permeability. IL-6 is a key factor in immune imbalance; hence it also serves as a target for drugs such as tocilizumab and sarilumab, which are currently on trial **[229]**.

G. Nucleoside analogues and protease inhibitors

Nucleoside analogues that have been approved or are under development may have the potential to treat novel coronavirus infections, including favipiravir, ribavirin, remdesivir and galidesivir. They are usually derivatives of adenine or guanine. They can be used by RNA-dependent RNA polymerase (RdRp) to synthesize RNA strands; however, when integrated into the RNA strand, they block the continued synthesis of the RNA strand, leading to an early termination of its synthesis. They can be used to treat a wide spectrum of RNA viruses, including coronaviruses. Some approved protease inhibitors such as disulfiram, lopinavir, and ritonavir show inhibitory activity against SARS-CoV and MERS-CoV. These results suggest that these drugs may be used to treat COVID-19. Likewise, the inhibitors towards SARS-CoV-2 Mpro, such as (S)-N-Benzyl-3-(S)-2-cinnamamido-3-cyclohexylpropanamido)-2-oxo-4-((S)-2-oxopyrrolidin-3-yl) butanamide (referred to as 11r), pyridone-containing α-ketoamide derivative of 11r (referred to as 13b) and nelfinavir, can also block virus infection **[23]**.

H. Anticoagulant therapy

Inflammatory factors and lymphocyte subsets are routinely monitored during the course of the disease. To enhance the immune function of patients and inhibit the formation of inflammatory factor storms, IVIg and low molecular weight heparin (LMWH) anticoagulant therapy could be given as early as possible when T cells, B cells, inflammatory cytokines, and D-Dimer show the following trends: Significantly lower T lymphocyte and B lymphocyte levels in peripheral blood than before, increase in inflammatory cytokines, abnormal increase in coagulation parameters such as D-dimer, and an indication of lung lesion expansion on chest CT. Specifically, high-dose IVIg at 0.3-0.5 g/kg weight of the patient per day for 5 days, and 100 U/kg weight of LMWH per 12h by subcutaneous injection for at least 3-5 days may be administered **[161]**.

Then, in order to avoid side effects after anticoagulant treatment, the indicators of laboratory results should be closely monitored.

It is recommended that targeted therapy be applied for COVID-19 patients with different degrees of coagulation dysfunction. For example, when patients experience coagulation dysfunction and liver failure, the plasma exchange should be used to clear some harmful substances and supplement coagulation factors **[235]**.

VI. PREVENTION

Initial SARS-CoV-2 prevention includes social distancing, the use of face masks, environmental hygiene, and hand washing. Although the most important pharmacologic interventions to prevent SARS-CoV-2 infection are likely to be vaccines, the repurposing of established drugs for short-term prophylaxis is another, more immediate option **[236]**.

A. Preventive measures

The application of preventive measures is intended to avoid infection and prevent secondary infections, interrupt human-to-human transmission and prevent further international spread.

And it starts by staying aware of the latest information on the COVID-19 outbreak, and following the directions of the local health authority **[237]**.

1. Individual measures

- Washing hands regularly and thoroughly with soap and water for at least 20 seconds or with an alcohol-based hand rub (hand sanitizer that contains at least 60% alcohol) especially after visiting a public place, or blowing your nose, sneezing or coughing.
- Wearing a facemask, especially in closed spaces, such as workplace, public transports, primary necessities suppliers (grocery stores, supermarkets).
- Avoiding touching nose, eyes or mouth with unwashed hands.

- Covering mouth and nose with a tissue paper whenever coughing or sneezing, and washing hands immediately after throwing the used tissues in the trash.
- Maintaining social distancing (at least 1m or 3 feet distance between 2 people) and avoiding close contact with anyone thought to be ill (coughing or sneezing: because COVID-19 can be transmitted through droplets.
- Avoiding large events and mass gatherings.

2. Collective measures

If infected, or thought to be ill, it is recommended:

- Seeking medical attention.
- Staying at home, to avoid infecting others.
- Staying isolated, if possible, in a separate room from the rest of the family and wearing a facemask when around other people.
- Avoiding sharing bedding, dishes, glasses and other household items.
- Other recommended measure:
- Cleaning dirty surfaces using detergent or antiseptic soap and water before disinfection apply,
- Apply disinfectant daily on frequently touched surfaces, such as desks, phones, keyboards, toilets, faucets, tables, doorknobs, light switches, countertops, handles, and sinks.
- Avoiding direct physical contact (including physical examination and exposure) to respiratory and other body secretions **[237]**.

B. Chemoprophylaxis

Chemoprophylactics against emerging epidemic and pandemic infectious diseases offer potential for prevention but require efficacy and safety analysis before widespread use can be recommended **[238]**.

Some researchers have promoted chloroquine and hydroxychloroquine for the treatment and prevention of illness from a variety of microorganisms, including SARS-CoV-2 **[239]**.

Boulware *et al.* conducted a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada, testing hydroxychloroquine as post exposure prophylaxis for COVID-19.

Were enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed COVID-19 contact. The incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 (11.8%)) and those receiving placebo (58 of 407 (14.3%)) **[240]**.

In Morocco, the Ministry of Health issued a guideline detailing the management protocol for patients with COVID-19 and their contacts, dated April 7, 2020. (Appendix *Figure 6*).

The note recommended a 5-day prophylactic treatment for high-risk contacts with hydroxychloroquine, at a dose of 400mg twice a day on day 1, then 200mg twice a day from day 2 to day 5 **[112]**.

C. Vaccine research

As many countries continue to battle with new infections caused by coronavirus disease 2019 (COVID-19), vaccine development has been accelerated to achieve immunity to the virus and stop transmission. The process of vaccine development is usually long and tedious (*Figure 29*). The recent advances in COVID-19 vaccine development have indicated that research innovations are accumulative, building on already existing knowledge. This allows for the pandemic speed at which the COVID-19 vaccines have been rapidly developed. Vaccines are biological preparations that provide active acquired immunity to a particular infectious disease. They do so by stimulating an immune response to an antigen, a molecule found on the pathogen. Vaccines date back to the era of Edward Jenner who developed the smallpox vaccine in 1796 **[241]**.

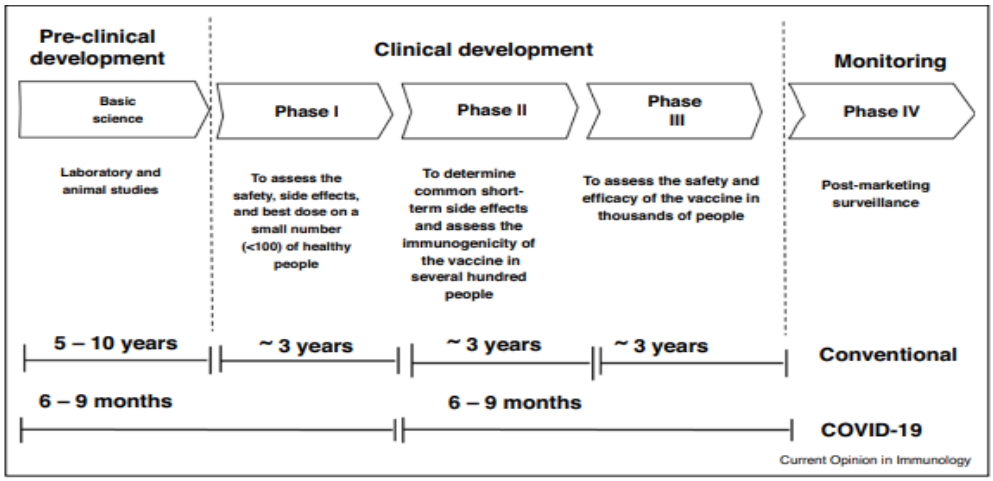


Figure 29: *COVID-19 vaccine development compared to conventional vaccine development* **[241]**.

1. COVID-19 vaccines

In the history of vaccines, COVID-19 vaccines have accelerated at an unimaginable speed. Currently, there are 184 candidate vaccines in preclinical development and 104 in clinical stages of development. Recent data indicate that there are 18 COVID-19 vaccines approved and are currently in use around the world **[241]**. The COVID-19 vaccines are in four primary categories using different platforms: whole virus vaccines, protein-based vaccines, viral vector vaccines, and nucleic acid vaccines **[242]**.

a) Whole virus vaccines

Whole virus vaccines use a weakened (attenuated) or inactivated form of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to trigger protective immunity. Live attenuated vaccines use a weakened form of the virus, which can still grow and replicate but does not cause illness **[242]**. Inactivated vaccines contain viruses whose genetic material has been destroyed by heat, chemicals, or radiation, so they cannot infect cells and replicate but can still trigger an immune response **[243]**. Both types of whole virus vaccines are tried and tested vaccine approaches, which form the basis of many existing vaccines. Existing live attenuated virus vaccines include measles, oral poliovirus, and yellow fever vaccines; and inactivated vaccines include inactivated polio and seasonal influenza vaccines **[244]**. There are currently 16 inactivated and two live attenuated candidate SARS-CoV-2 vaccines in clinical development. The advantages of live-attenuated SARS-CoV-2 vaccine candidates include targeting and stimulating robust mucosal and cellular immunity, which is essential for protection without the need for adjuvants. However, this type of vaccine has some disadvantages. SARS-CoV-2 is excreted in the feces of infected patients

[245][246] and there is concern that live-attenuated SARS-CoV-2 vaccines may be excreted in the feces of vaccines, possibly leading to SARS-CoV-2 transmission to unvaccinated individuals. The use of live-attenuated SARS-CoV-2 vaccine may also increase the risk of recombination between the vaccine strain and circulating wild-type virus, generating new viral variants. In addition, production and formulation of a live attenuated SARS-CoV-2 vaccine is labor-intensive and requires rigorous quality control, which would slow down large-scale vaccine production. At least two SARS-CoV-2 inactivated candidate vaccines have been approved for emergency use **[241]**.

b) Protein-based vaccines

There are two types of protein-based vaccines, that is, subunit and virus-like particle vaccines. Protein subunit vaccines consist of viral antigenic fragments produced by recombinant protein techniques. They are easy to produce, and relatively safe and well-tolerated compared to whole virus vaccines. The limitation of protein subunit vaccines is their low immunogenicity **[247]**. Therefore, adjuvants are usually used together with subunit vaccines to improve immunogenicity. Existing subunit vaccines include those against whooping cough, Streptococcus pneumoniae, and Haemophilus influenzae type b **[242]**. There are currently 33 SARS-CoV-2 protein subunit candidate vaccines in clinical development, with at least one that has been shown in phase III clinical trials to induce high titers of neutralizing antibodies **[248]**. Beyond subunit vaccines, other protein-based SARS-CoV-2 candidate vaccines use empty virus shells that mimic the coronavirus structure but are not infectious because they lack genetic material; referred to as ‘virus like particles’ **[249]**. There are currently five virus-like particle vaccines in clinical development. Existing vaccines that use this technology include human papillomavirus vaccines **[250]**.

c) *Viral vector vaccine*

Viruses survive and replicate by invading their host's cells and hijacking their protein-making machinery, so it reads the virus genetic code and makes new viruses. These virus particles contain antigens, molecules that can trigger an immune response **[245]**. A similar principle underpins viral vector vaccines, where the host cells only receive a code to make specific antigens. The viral vector acts as a delivery system, providing a means to invade the cell and insert the code for SARSCoV-2 antigens. The virus used as a vector is chemically weakened so that it cannot cause disease. In this way, the body can mount an immune response safely, without developing the disease **[247][251]**. Viruses that have been used as vectors include the adenovirus (that causes common cold), measles virus, and vaccinia virus. There are two categories of viral vectors; those that can still replicate within cells and those that cannot because key genes have been disabled **[242][244][251]**. Before the onset of SARS-CoV-2, only one viral vector vaccine had been approved for use in human population against Ebola virus disease **[252]**. The Ebola vaccine uses the vesicular stomatitis virus as a replicating viral vector. One drawback with viral vector vaccines is that if people have been previously exposed to the viral vector and have developed an immune response against it this could potentially blunt the vaccine's effectiveness **[249]**. There are currently 16 non-replicating and two replicating viral vector candidate SARS-CoV-2 vaccines in clinical development. Various viral vector SARS-CoV-2 candidate vaccines, all using non-replicating viral vectors, have been approved by regulatory authorities around the world for emergency use **[241]**.

d) Nucleic acid vaccines

SARS-CoV-2 nucleic acid vaccines use genetic instructions, in the form of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), for a SARS-CoV-2 protein that prompts an immune response. Before COVID-19, this platform was unproven, as no existing licensed vaccine used this technology. DNA vaccines use a piece of DNA encoding the antigen, which is first inserted into a bacterial plasmid. Bacterial plasmids are circular pieces of DNA used to store and share genes that may benefit their survival **[253]**. Plasmids can replicate the main chromosomal DNA independently and provide a simple tool for transferring genes between cells. Because of this, they are already widely used in genetic engineering. This allows for the host machinery to translate the antigen message into protein inside cells **[251]**. RNA vaccines, on the other hand, encode the antigen of interest in a messenger RNA (mRNA) or self-amplifying RNA, which is a molecular template used by cellular factories to produce proteins **[251][253]**. The RNA can be injected by itself, encapsulated within nanoparticles, or driven into cells using some of the same techniques developed for DNA vaccines. Once the DNA or RNA is inside the cell and starts producing antigens, these are then displayed on its surface, where they can be detected by the immune system, triggering a response. This response includes killer T cells (which look for and kill infected cells) and antibody-producing B cells and helper T cells that support antibody production **[244][247]**. There are currently at least 10 DNA and 18 RNA candidate vaccines in clinical development. Several mRNA vaccines against SARS-CoV-2 have been approved for emergency use around. This is the first time in the history of vaccinology that a nucleic acid vaccine has been approved for use in public health programs **[241]**.

2. COVID-19 vaccine rollout

By the end of 2021, nearly eight billion doses of COVID-19 vaccines had been administered worldwide. 54.2% of the world population had received at least one dose of a COVID-19 vaccine, and 42.7% is fully vaccinated.

By the same time, nearly 30 million COVID-19 vaccine doses were being administered each day worldwide. Countries that had fully vaccinated their citizens by the end of 2021 include the United Arabs Emirates, Singapore, Cuba, Portugal, Chile, China, South Korea, Spain, Canada, Japan, Italy, France, Brazil, United Kingdom, Germany, and United States. However, only 5.8% of people in low-income countries had received a COVID-19 vaccine dose by then.

In Morocco, the vaccination campaign started on February 19th, 2020.

As of the end of November 2021, 22.69 million people are fully vaccinated, which represents 61% of the citizens, and more than 48 million vaccine doses had been administered, which makes it the first African country with the highest proportion of vaccinated population **[5]**.

Table 15: *Summary of treatment methods for COVID-19 based on different mechanisms* **[161].**

Mechanisms or methods	Drugs or agents
Oxygen therapy	Mixed inhalation of hydrogen and oxygen (H_2/O_2:66.6%/33.3%), (31) extracorporeal membrane oxygenation technology (15).
Immunotherapy	Convalescent patient plasma, (15) monoclonal antibodies, (45) interferon, immunomodulatory agents (baricitinib, imatinib, dasatinib, and cyclosporine) (41)
Virus blocking and pathway inhibitors	Resorcinolnaphthalein, 1-[(2-dimethylamino)ethylamino]-4-(hydro xymethyl)-7-[(4-methylphenyl)sulfonyloxy]-9H-xanthene-9-one, (47) ACE inhibitors, AT1R inhibitors, (48) APN01, camostat, nafamostat, bromhexine, aprotinin, chlorpromazine, baricitinib, ruxolitinib (7), MK-2206, niclosamide, diltiazem, nitazoxanide, tizoxanide, valinomycin, the inhibitor of ERK/MAPK and PI3K/AKT/mTOR signaling pathways (sirolimus, everolimus, metformin) (7).
Suppression of cytokine storms and bacterial infections	Artificial liver blood purification techniques(CRRT, blood/plasma perfusion, absorption, plasma replacement), (47,49) non-steroidal anti-inflammatory medication, immunosuppressants, IFN-λ, corticosteroids, the cytokine antagonists, blockers and inhibitors, intravenous immunoglobulin, mesenchymal stem cells, sphingosine-1-phosphate receptor 1 agonist, increased vascular permeability, (52-54) tocilizumab, sarilumab, microecological regulators combined with Traditional Chinese Medicine (55)
Nucleoside analogues and protease inhibitors	Favipiravir, ribavirin, remdesivir and galidesivir, disulfiram, lopinavir, ritonavir, (55,56) inhibitors towards SARS-CoV-2 M^{pro}[(S)-N-Benzyl-3-((S)-2-cinnamamido-3-cyclohexylpropanamido)-2-oxo-4-((S)-2-oxopyrrolidin-3-yl) butanamide (referred to as 11r), pyridone-containing α-ketoamide derivative of 11r (referred to as 13b), nelfinavir] (7)
Anticoagulant therapy	IVIg, low molecular weight heparin, plasma exchange (44,50)
Vaccine research	RNA vaccines (LNP-encapsulated mRNA, LNP-encapsulated mRNA encoding RBD, LNP encapsulated mRNA cocktail encoding VLP), DNA vaccines (ChAdOx1 nCoV-19, INO-4800), vaccines based on protein subunit, viral vector virus-like particles, inactivated virus, live attenuated virus (59-61)

CRRT, continuous renal replacement therapy; IVIg, intravenous immunoglobulin; LNP, lipid nanoparticles; RBD, receptor binding domain; VLP, virus-like particles; ERK/MAPK, extracellular regulated protein kinases/mitogen activated protein kinase; PI3K/AKT/mTOR, phosphatidylinositol 3 kinase/protein kinase B/mammalian target of rapamycin; AT1R, angiotensin II type1receptor.

VII. PROGNOSIS

In our study, our patients were ranked according to the NEWS severity score.

84 patients (45.2%) were asymptomatic, 35 (18.8%) were mild, 62 (33.3%) were moderate, 5 (2.7%) cases were severe, and none of our patients belonged to the critical group.

The prognosis of most patients is good, with only a few patients being reported as critically ill, and the mortality rate ranging from 0 to 14.6%. However, the prognosis of the elderly and those with underlying chronic diseases is poor **[161]**.

The global hospital mortality from COVID-19 is approximately 15% to 20%, but can be as high as 40% in patients requiring ICU admission. However, mortality rates fluctuate across cohorts, reflecting differences in the testing completeness and case identification, variable thresholds for hospitalization, and differences in outcomes.

Hospital mortality ranges from less than 5% among patients younger than 40 years, to 35% for patients aged 70 to 79 years, and more than 60% for patients aged 80 to 89 years **[237]**.

It should be noted that some factors could influence the prognosis of COVID-19 patients **[161]**.

- ***Changes in laboratory results:*** By analyzing the entire course of treatment of a patient for COVID-19, it can be concluded that as the treatment progresses, the body temperature of the patient returns to normal, other clinical symptoms are significantly reduced and the levels of cytokines such as IL-2, IL-6, IL-7 and TNF alpha decrease gradually **[254]**. In addition, after effective treatment, the levels of white blood cell (WBC), lymphocyte, CRP, D-dimer, ESR, and other indicators in the blood become normal. However, if these laboratory results are abnormal, the patients may have poor prognosis. As reported, cytokine storms occur in critically ill patients. Therefore, in the later stage of the disease, high levels of cytokines suggest a poor prognosis. The concomitant AKI is also a factor for poor prognosis. Additionally, the viral load reflected in the results of RT-PCR can also be used to predict the prognosis, for the heavy viral load may lead to poor prognosis, and the number and the dynamic changes of platelets and platelet-to-lymphocyte ratio (PLR) were also worthy of attention in severe cases. A high PLR may indicate poor prognosis **[255]**.

- ***Changes in CT findings:*** In a SARS-CoV-2 infection, the imaging features and total CT score vary throughout the course of the disease, from initial diagnosis until patient recovery. Most patients showed the greatest severity of lung disease on CT around 10 days after initial onset of symptoms. Improvement in chest CT reports began around 14 days after the onset of initial symptoms **[256]**. Patients with mild disease showed less inflammation and injury to lungs when compared with critically ill patients **[257]**. According to the analysis of imaging features, pleural effusion is rare in cases of COVID-19. Hence, the presence of

pleural effusion and diffuse alveolar damage patterns might suggest poor prognosis, as do the high incidences of consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, lymph node enlargement and pericardial effusion **[258][259]**. In summary, analysis of CT findings might be useful to predict the clinical outcome and patient prognosis. If clinicians can deduce specific patterns of lung abnormalities from CT scans, patient prognosis can be efficiently predicted **[161]**.

- ***Serum antibodies and the titer:*** The plasma from recovered patients can be used to treat critically ill patients because of the viral specific antibodies present in the plasma. Since the antibodies have protective effects, they can help to resist the invasion of SARS-CoV-2 again. Therefore, the antibodies and their titer can also be used to predict the prognosis of the disease **[161]**.
- ***Disseminated intravascular coagulation (DIC):*** Disseminated intravascular coagulation frequently occurred in patients with COVID-19 with serious respiratory failure, and was considerably more frequent in non-survivors (71.4%) compared with survivors (0.6%) (12,84). These results provide evidence that DIC can be listed as a prognostic parameter of COVID-19 **[161]**.
- ***Individual factors:*** Differences in host susceptibility to viruses and immune systems can also be considered as important prognostic factors. Recently, some studies show that cardiovascular diseases such as hypertension increased the incidence and severity of coronavirus infection. Also, myocardial injury caused by coronavirus infection contributed to poor prognosis. At the same time, diabetes or some other comorbidities, and the time span between illness onset and antiviral

treatment are major factors influencing the prognosis. Age also plays a significant role in prognosis. Patients above the age of 65 are at a higher risk of disease progression **[161]**.

Table 16: *Factors influencing the prognosis of COVID-19* **[161]**.

Classification	Factors
Changes in laboratory results	Body temperature and other clinical symptoms, cytokine levels, the levels of WBC, lymphocyte, CRP, D-dimer, ESR and other indicators (62), acute kidney injury, the ratio of $CD4^+$ T cells to $CD8^+$ T cells (69), the number and the dynamic changes of platelets, platelet-to-lymphocyte ratio (PLR) (70).
Changes in CT findings	Pleural effusion, diffuse alveolar damage pattern, consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, lymph node enlargement, pericardial effusion (74).
Serum antibodies and titer	Specific IgG, IgM (53)
Individual factors	Cardiovascular disease, myocardial injury, diabetes or some other comorbidities (75,76), time from illness onset to antiviral treatment, age (77), level of (HFABP) (78).
Complications	Disseminated intravascular coagulation (79,80).

WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IgM, immunoglobulin M; HFABP, heart-fatty acid binding protein.

VIII. EVOLUTION AND OUTCOME

In our study, all our patients recovered completely and were discharged.

The clinical cure, retained on the disappearance of clinical symptoms and apyrexia for more than 3 days, after 2 weeks of well conducted treatment, was obtained in 184 patients representing 98.9% of the study population.

51 patients (27.4%) had an early virologic clearance, as in they were tested negative on the 6^{th} and 8^{th} day respectively, while 135 patients (72.6%) were not, and kept being tested until negativity.

The longest hospitalization duration was 38 days.

7 patients required oxygen therapy (3.8%), and 1 patient (0.5%) was transferred to intensive care unit for 48 hours, and was discharged afterwards.

No deaths were reported.

Following systematic treatment, clinical symptoms of the patients gradually improve until they recover.

Usually, patients meet the criteria for discharge from isolation or hospitals when their respiratory pathogenic nucleic acid tests show two consecutive negatives results (the sampling interval should be at least one day) **[260]**.

According to ***Zhou*** *et al.*, among 191 patients, 54 (28.3%) patients died during hospitalization and 137 (71.7%) were discharged. The median time from illness onset (i.e., before admission) to discharge was 22 days [18–25], whereas the median time to death was 18.5 days [15–22]. 32 patients required invasive mechanical ventilation, of whom 31 (97%) died. The median time from illness onset to invasive mechanical ventilation was 14.5 days [12–19].

Sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, heart failure, and septic shock. Half of non-survivors experienced a secondary infection, and ventilator-associated pneumonia occurred in 10 (31%) of 32 patients requiring invasive mechanical ventilation. The frequency of complications was higher in non-survivors than survivors **[153]**.

According to ***Zhang*** *et al.*, 251 patients among 663 (37.9%) improved in hospital during follow-up. Older patients (> 60 years) were more prone to have no improvement than others (<60 years old). Among the patients with improvement, 103 (251, 41%) were men. Moreover, 198 patients with improvement (251, 78.9%) had no coexisting chronic disease, which is significantly higher than patients without improvement (219, 53.2%) **[160]**.

IX. STATISTICAL STUDY

In the univariate analysis, the asymptomatic infection (45.2%) was significantly associated to a normal CT scan ($p < 0.0001$), a normal CRP level ($p < 0.001$), a normal ferritin level ($p < 0.002$) and the absence of lymphopenia ($p < 0.03$).
Normal CT scan (53.2%) was significantly linked to the age under 40 years old ($p < 0.0001$), asymptomatic cases ($p < 0.0001$), a time to diagnosis under 5 days in the symptomatic patients ($p < 0.019$), a normal CRP level ($p < 0.0001$), a normal LDH level ($p < 0.005$) and the absence of lymphopenia ($p < 0.0001$). (Appendix *Table 9* and *10*).

In the multivariate analysis, the asymptomatic infection was significantly associated to a normal CT scan ($p < 0.009$).
And regarding normal CT scan, it was significantly linked to the age under 40 years old ($p < 0.004$), asymptomatic patients ($p < 0.002$), a normal CRP level ($p < 0.001$), the absence of lymphopenia ($p < 0.01$) and an early virologic clearance ($p < 0.043$) (Appendix *Table 11* and *12*).

It appears that there is a significant correlation between clinical and CT scan data, as asymptomatic patients are more likely to present with normal CT scan findings.

Conclusion

Through our objective which was to study the clinical and radiological characteristics of patients with COVID-19, and to establish a possible correlation between these features, as well as to highlight potential associated factors to both parameters, we conducted a retrospective study in the Center for Virology, Infectious and Tropical Diseases, Mohammed V Military Teaching Hospital, involving 186 cases whose diagnosis was confirmed by RT-PCR, between March and June 2020.

Our results showed that:

- ✓ In the univariate analysis, patients with an asymptomatic presentation are more likely to have a normal CT scan a normal CRP level, a normal ferritin and a normal of lymphocytes count.

  And patients with normal CT scan findings are more likely to be under 40 years of age, asymptomatic, with a time to diagnosis under 5 days if symptomatic, have a normal CRP level, a normal LDH level and a normal lymphocytes count

- ✓ In the multivariate analysis, the asymptomatic infection was significantly associated to a normal CT scan.

  And patients with normal CT scan, are more likely to be under 40 years old, asymptomatic, have a normal CRP level, normal lymphocytes count and an early virologic clearance.

Thus, it appears that there is a significant correlation between clinical and CT scan features.

From these findings, the prognosis of the patients can be predicted, since asymptomatic cases, with a normal CT scan and an undisturbed biological profile are at the least risk of developing severe forms of COVID-19 related ARDS.

Abstract

ABSTRACT

Title: Clinical and CT scan features of COVID-19 patients admitted to the Center for Virology, Infectious and Tropical Diseases. About 186 cases.

Author: MOUTMIR Yasmine.

Keywords: COVID-19, clinical features, CT scan features

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, responsible of the pandemic that is currently raging on, and that initially emerged in China in December 2019.

It represents, not only a major threat to global public health, but also a huge economic burden and panic to society.

Around 80% of the infected subjects will experience only mild to moderate symptoms. However, in 10 to 20% of cases, the clinical presentation happens to be much more critical, requiring specific management, mainly in elderly subjects and those with associated comorbidities.

Our work, which aimed to describe the clinical, biological and morphological

presentation of the first COVID-19 cases, to establish a possible correlation between the clinical and morphological features on CT scan, and to define the predictive factors of an unfavorable outcome, focused on a retrospective descriptive and analytical study about 186 cases from March through June 2020.

Our study showed predominance in the age group between 25 and 39 years old, with a median age of 34 years old, as well as a higher prevalence among males (90.9%) compared to females (9.1%) with a sex ratio of 9.94.

10.8% had comorbidities, with hypertension being the most common comorbidity, followed by asthma, diabetes and heart disease.

45.2% of the patients were asymptomatic, and 53.2% had normal a CT scan.

And our study found out a significant correlation between clinical and CT scan data, as asymptomatic patients are more likely to present with normal CT scan findings.

All our patients recovered and were discharged, and no deaths were reported.

RÉSUMÉ

Titre : Aspects cliniques et morphologiques des patients COVID-19 admis au Centre de Virologie, de Maladies Infectieuses et Tropicales. A propos de 186 cas.

Auteur : MOUTMIR Yasmine.

Mots clés : COVID-19, aspects cliniques, aspects morphologiques.

Le COVID-19 est une maladie infectieuse causée par le virus SARS-CoV-2, responsable de la pandémie qui sévit actuellement, et qui a initialement émergé en Chine en Décembre 2019.

Elle représente non seulement une grande menace pour la santé publique mondiale, mais aussi un fardeau économique important et une source de panique pour la société.

C'est une maladie bénigne dans environ 80% des cas. Cependant, dans 10 à 20% des cas, le tableau clinique peut être beaucoup plus sévère, nécessitant une prise en charge spécifique, essentiellement chez les sujets âgés, ou avec comorbidités.

Notre travail, qui avait pour objectif de décrire la présentation clinique, biologique et morphologique des premiers cas confirmés, d'établir une éventuelle corrélation entre les caractéristiques cliniques et morphologiques au scanner, et de définir les facteurs prédictifs d'une évolution défavorable, a consisté en une étude rétrospective descriptive et analytique portant sur 186 cas entre Mars et Juin 2020.

Notre étude a montré une prédominance dans le groupe d'âge des 25 à 39 ans, avec une médiane d'âge de 34 ans, ainsi qu'une prévalence plus élevée chez les hommes (90.9%) par rapport aux femmes (9.1%) avec un sex ratio de 9.94.

10.8% présentaient des comorbidités, l'hypertension artérielle étant la comorbidité la plus fréquente, suivie de l'asthme, du diabète et des cardiopathies.

45.2% des patients étaient asymptomatiques et 53.2% avaient un scanner normal.

Notre étude a révélé une corrélation significative entre les données cliniques et morphologiques, les patients asymptomatiques étant plus susceptibles de présenter un scanner normal.

Tous nos patients ont guéri, et aucun décès n'a été signalé.

ملخص

العنوان: الجوانب السريرية والمورفولوجية لمرضى كوفيد-19المعالجون بمركز علم الفيروسات والأمراض التعفنية و الاستوائية. بصدد 186 حالة.

من طرف: متمير ياسمين.

الكلمات المفتاحية: كوفيد-19، الجوانب السريرية، الجوانب المورفولوجية.

كوفيد- 19 هو مرض معد يسببه فيروس كورونا المستجد والمسؤول عن الجائحة الحالية التي ظهرت في البداية في الصين في دجنبر 2019.

إنه لا يمثل تهديدًا كبيرًا للصحة العامة العالمية فحسب، بل يمثل أيضًا عبئًا اقتصاديًا كبيرًا ومصدرًا للذعر للمجتمع.

إنه مرض طفيف بالنسبة لحوالي 80٪ من الحالات، إلا أنه في 10 إلى 20٪ من الحالات يمكن أن تكون الصورة السريرية أكثر حدة خاصة عند كبار السن أو في حالات الاعتلال المتزامن، متطلبة بذلك عناية خاصة.

عملنا الذي يهدف إلى وصف الجوانب السريرية والبيولوجية والمورفولوجية للحالات المؤكدة الأولى، إيجاد ارتباط محتمل بين الخصائص السريرية والمورفولوجية على مسح التصوير المقطعي، وتحديد العوامل التنبؤية للتطور السلبي، يتألف من دراسة وصفية وتحليلية بأثر رجعي بصدد 186 حالة بين مارس ويونيو 2020.

أظهرت دراستنا هيمنة الفئة العمرية من 25 إلى 39، بمتوسط 34 سنة بالإضافة إلى انتشار أعلى لدى الرجال (90.9٪) مقارنة بالنساء (9.1٪) بنسبة جنسية تبلغ 9.94.

10.8٪ يعانون من أمراض مصاحبة، إذ أن ارتفاع ضغط الدم الشرياني هو أكثر الأمراض المصاحبة شيوعا، يليه الربو والسكري ثم أمراض القلب.

45.2٪ من المرضى كانوا بدون أعراض، و53.2٪ كان لديهم مسح التصوير المقطعي عادي.

أبانت دراستنا عن وجود علاقة كبيرة بين البيانات السريرية والمورفولوجية، حيث أن كشف مسح التصوير المقطعي له قابلية ان يكون عاديا عند المرضى بدون أعراض.

تعافى جميع مرضانا، ولم يتم الإبلاغ عن أي وفيات.

Appendix

Table 1: *Detailed taxonomic structure of the Coronaviridae family* **[22]**.

Genus	Subgroup/ Lineage	Abbreviation	Genome	Species	Disease Name	Organ System
Alphacoronavirus		PEDV	28,033	Porcine	Porcine epidemic diarrhea virus	Enteric
Alphacoronavirus		TGEV	28,586	Porcine	Transmissible gastroenteritis virus	Enteric
Alphacoronavirus		FIPV	29,355	Feline	Feline coronavirus	FIP
Alphacoronavirus		CCoV	29,363	Canine	Canine coronavirus	Enteric
Alphacoronavirus		PRCV	27,550	Porcine	Porcine respiratory coronavirus	Respiratory
Alphacoronavirus		HCoV-229E	27,317	Human	Common cold	Respiratory
Alphacoronavirus		HCoV-NL63	27,553	Human	Common cold	Respiratory
Alphacoronavirus		Rh-BatCoV-HKU2	27,165	Bat		
Alphacoronavirus		Mi-BatCoV 1A	28,326	Bat		
Alphacoronavirus		Mi-BatCoV 1B	28,476	Bat		
Alphacoronavirus		Mi-BatCoV-HKU8	28,773	Bat		
Alphacoronavirus		Sc-BatCoV-512	28,179	Bat		
Betacoronavirus	A	HCoV-OC43	30,738	Human	Common cold	Respiratory
Betacoronavirus	A	BCoV	31,028	Bovine	Calf diarrhea, winter dysentery, BRD	Enteric and respiratory
Betacoronavirus	A	PHEV	30,480	Porcine	Chronic wasting, encephalomyelitis	Enteric and neurological
Betacoronavirus	A	AntelopeCoV	30,995	Antelope		
Betacoronavirus	A	GiCoV	30,979	Giraffe		Enteric
Betacoronavirus	A	ECoV	30,992	Equine	Equine coronavirus	Enteric
Betacoronavirus	A	MHV	31,357	Mouse	Mouse hepatitis virus	Hepatic
Betacoronavirus	A	HCoV-HKU1	29,926	Human		Respiratory
Betacoronavirus	A	RCoV	31,250	Rat		Respiratory
Betacoronavirus	B	SARS CoV	29,751	Human	Severe acute respiratory syndrome	Respiratory
Betacoronavirus	B	SARSr-CiCoV	29,728	Human	Severe acute respiratory syndrome	Respiratory
Betacoronavirus	B	SARSr-Rh-BatCoV HKU3	29,704	Bat	Chinese horseshoe bat	
Betacoronavirus	B	SARSr CoV CFB	29,734	Human	Severe acute respiratory syndrome	Respiratory
Betacoronavirus	C	Ty-BatCoV-HKU4	30,286	Bat		
Betacoronavirus	C	Pi-BatCoV-HKU5	30,488	Bat		
Betacoronavirus	D	Ro-Bat-CoV HKU9	29,114			
Gammacoronavirus		IBV	27,608	Chickens	Avian infectious bronchitis virus	Respiratory
Gammacoronavirus		TCoV	27,657	Turkey	Bluecomb, turkey coronavirus	Enteric
Gammacoronavirus		BWCoV-SW1	31,686	Whale	Beluga whale CoV	
Deltacoronavirus		BuCoV HKU11	26,476	Avian	Bulbul coronavirus	
Deltacoronavirus		ThCoV HKU12	26,396	Avian	Thrush coronavirus	
Deltacoronavirus		MunCoV HKU13	26,552	Avian	munia coronavirus	
Deltacoronavirus		PorCoV HKU15	25,421	Porcine	Porcine coronavirus	Enteric
Deltacoronavirus		WECoV HKU16	26,027		White eye coronavirus	
Deltacoronavirus		SpCoV HKU17	26,067	Avian	Sparrow coronavirus	
Deltacoronavirus		MRCoV HKU18	26,674	Avian	Magpie robin coronavirus	
Deltacoronavirus		NHCoV HKU19	26,064	Avian	Night heron coronavirus	
Deltacoronavirus		WiCoV HKU20	26,211		Wigeon coronavirus	
Deltacoronavirus		CMCoV HKU21		Avian	Common moorehen	

Table 2: *Cleavage products of coronavirus replicase polyproteins pp1a and pp1b: names, assigned functions and structure* **[261].**

Protein	Assigned function	E/N*	MMDB ID
nsp1†	IFN antagonist	N	ND
	Degradation of host mRNAs		
	Inhibition of translation		
	Cell cycle arrest		
nsp2	Unknown; associates with RTCs	N	ND
nsp3	Papain-like proteinase $PL1^{pro}$; polyprotein processing	N	37505; 42180
	Papain-like proteinase $PL2^{pro}$; polyprotein processing, DUB	E	
	ADP-ribose-1″phosphatase (macrodomain); RNA-binding	N	
	IFN antagonist		
	DMV formation?		
nsp4	Unknown; DMV formation?		76092
nsp5	Main proteinase M^{pro}; polyprotein processing	E	20276; 23158
nsp6	Unknown; DMV formation?		ND
nsp7	ssRNA binding		36090
nsp8	Noncanonical "secondary" RdRp with putative primase activity; forms hexadecameric supercomplex with nsp7		36090
nsp9	ssRNA binding; associates with RTCs		26498; 60895
nsp10	Dodecameric zinc finger protein; associates with RTCs, stimulates nsp16 methyltransferase activity		40869; 40904
nsp11	Unknown		ND
nsp12	RdRp	E	ND
nsp13	Helicase	E	ND
	RNA 5′-triphosphatase		
nsp14	3′→5′exoribonuclease (required for RdRp fidelity)	N	ND
	Guanine-N7-methyltransferase (RNA cap formation)	N	
nsp15	Hexameric uridylate-specific endoribonuclease	N	40936
nsp16	Ribose-2′-*O*-methyltransferase (RNA cap formation)	N	ND

MMDB ID numbers are listed for replicase proteins for which crystal structures are available. IFN, interferon; RTC, replicase/transcriptase complex; DUB, deubiquitinating enzyme; DMV, double-membrane vesicles.
*Essential (E) or non-essential (N) for replication in cultured cells.
†Absent in gammacoronaviruses.

A

ROYAUME DU MAROC

Ministère de la Santé

Le Ministre

المملكة المغربية

وزارة الصحة

الوزير

Circulaire N° 1 032 DELM/2020

17 AVR. 2020

Mesdames et Messieurs les Directeurs Régionaux de la Santé

Objet : Les mesures de suivi et de protection des professionnels de santé face à l'exposition au risque du Covid-19.

En plus des dispositions citées dans la circulaire n° 21 DELM/2020 sur les mesures d'hygiène et de sécurité relatives à la prévention du risque Covid-19 dans les structures administratives du Ministère de la Santé, j'ai l'honneur de vous demander de veiller à ce que les règles, ci-après, soient strictement appliquées au profit du personnel de soins relevant de votre région.

1. Information et formation sur le risque Covid-19

Des formations et des séances de sensibilisation doivent être dispensées à l'ensemble des professionnels des établissements de soins. Le contenu des séances devra être adapté au profil des différentes catégories du personnel (soins, transport sanitaire, hygiène hospitalière, etc.).

Les formations doivent être organisées en petits groupes respectant les règles d'espacement requis et doivent comprendre notamment :

- Le port des équipements de protection individuelle (EPI).
- Le respect des mesures d'hygiène et de sécurité collective et individuelle.

2. Mesures de protection spécifiques

a. Respect de la tenue vestimentaire professionnelle et le port des EPI conformément aux recommandations du Ministère de la Santé.

b. Exclusion des femmes enceintes et des professionnels de santé présentant des maladies chroniques **sévères** ou entrainant **une déficience immunitaire** de tout contact avec des patients atteints de Covid-19.

c. Un suivi médical des professionnels de soins en charge des malades atteints de Covid-19 doit être assuré par un système d'auto-surveillance. Il comporte notamment la prise de température deux fois par jour et l'observation de l'apparition des signes cliniques de la maladie.

d. Tout professionnel de santé présentant une symptomatologie respiratoire similaire à celles de l'infection au SARS-CoV-2 doit arrêter toute activité professionnelle et mis à l'isolement. Un examen médical doit être réalisé avec un test à la recherche du virus.

335, Av. Mohammed V, Rabat / Tél : 0537 76 11 21 - Fax : 0537 76 84 01 / www.sante.gov.ma

B

e. Démarrer la chimio-prophylaxie post-exposition avec de l'Hydroxychloroquine chez le personnel de santé ayant prodigué des soins, sans mesure de protection, à un patient COVID-19 confirmé selon le protocole suivant :

- La posologie : Hydroxychloroquine 200 mg à raison de 2 comprimés deux fois par jour à j1, puis 1 comprimé de 200mg matin et soir de J2 à J5.
- Le consentement éclairé du professionnel de santé est indispensable avant le début de ce traitement.
- Un bilan initial doit être réalisé et comportant au minimum un électrocardiogramme et un ionogramme.
- Un test doit être réalisé chez tout professionnel de santé ayant été en contact avec un cas de Covid-19 sans protection, 4 jours après le contact.
  Si le test est revenu négatif et le professionnel est asymptomatique, ce dernier rejoint son travail en portant un masque FFP2 lors de l'exercice de ses activités.

f. En cas de confirmation du test chez un professionnel de santé, une prise en charge doit être assurée immédiatement conformément aux procédures en vigueur.

g. Adoption d'une organisation de travail répondant aux exigences de la situation actuelle et permettant le maintien d'un meilleur niveau de quiétude et de motivation des professionnels de santé, comme par exemple, le travail avec des équipes alternatives, la répartition équitable de la charge du travail et le respect des temps de repos réparateur.

3. Activités d'alerte, d'information et de suivi médical

Une équipe constituée par le médecin de travail et un membre du CLIN de l'hôpital chef-lieu, ou une équipe désignée à cet effet procédera à cette activité.

A cet effet, la collecte de l'information sur le suivi médical des professionnels de soins en charge des malades atteints de Covid-19 doit répondre au modèle ci-joint (annexe 1).

Une enquête épidémiologique particulière et approfondie autour de chaque cas parmi les **professionnels de santé atteints de Covid-19** doit être entreprise. La collecte d'information sera faite par le biais d'une fiche dédiée à cet effet (annexe 2). Cette fiche doit être scannée et envoyée à la DELM sur l'adresse email suivant : delmdirection@gmail.com. Elle sera saisie sur l'application des cas positifs par l'intermédiaire d'une interface dédiée.

Un rapport hebdomadaire de la situation doit être établi et transmis à la DELM selon le canevas ci-joint (annexe 3) sur l'adresse e-mail de la DELM mentionnée ci-dessus.

Aussi et, compte tenu de l'importance de ces mesures dans la protection de nos professionnels de santé, vous demanderai-je de prendre toutes les dispositions nécessaires pour les mettre en œuvre en urgence.

Ministre de la Santé

Khalid AIT TALEB

Ampliation :
- Monsieur le Secrétaire Général
- Monsieur l'Inspecteur Général
- Madame et Messieurs les Directeurs de l'Administration Centrale
- Messieurs les Directeurs des Centres Hospitaliers Universitaires

Figure 1: *(A, B) Measures for the follow-up and protection of health professionals from exposure to COVID-19 (April 17th, 2020)* **[112]**.

CVMIT
Centre de virologie
Service de maladies infectieuses & tropicales

ROYAUME DU MAROC
FORCES ARMEES ROYALES
HOPITAL MILITAIRE D'INSTRUCTION MOHAMMED V - RABAT

Fiche d'investigation CoViD-19

Nom : **Prénom :** **Age :** **Sexe :**

Profession : Groupage : Tabac :

Comorbidité : Diabète ☐ HTA ☐ BPCO ☐ I. cardiaque ☐ I. rénale ☐

I. hépatique ☐ Néoplasie ☐ Déficit immunitaire ☐ Autres :

Date de début symptômes : **Date d'admission :**

CDD :

Clinique : fièvre ☐ céphalées ☐ rhinorrhée ☐ myalgie/asthénie ☐ toux ☐ diarrhée ☐

vomissements ☐ dyspnée ☐ Détresse respiratoire ☐ Tr neurologiques ☐ Autres :

FR : T° : SaO2 : TA : pouls :

Bilan :

Date								
GB								
PNN								
Lym								
Hb								
Pq								
CRP								
PCT								
D-dimère								
LDH								
Ferritine								
Troponine								
CPK								
ASAT/ALAT								
Creat								
Urée								

CVMIT Service de maladies infectieuses & tropicales (MIT)
Hospitalisation : ordinaire H.732 / confinement H.731
Flotte : médecin 06.703.76.312 / infirmier 063.74.80.096
E-mail : mit.hmim5@gmail.com
Centre de virologie, des maladies infectieuses et tropicales
Hôpital militaire d'instruction Mohammed V de Rabat

Figure 2: *Data Intake form (1st page).*

ECG
Rx thorax
TDM thoracique :

Autres :

Classification de la maladie : F. bénigne sans pneumonie ☐ Pneumonie simple ☐
Pneumonie hypoxémiante ☐ Pneumonie grave avec SDRA ☐

Traitement : Plaquenil ☐ Nivaquine ☐ azithromycine ☐ Lopinavir/r ☐ Remdesivir ☐
Actemra ☐ ATB :
Autres :

Evolution :

Passage en Réa : non ☐ oui ☐ si oui pourquoi ?

Contrôle virologique :

Date					
	J0	**J**	**J**	**J**	**J**
Pvt nasal					
Sérologie					
Virémie					

Décès ☐ Retour à domicile ☐ durée du séjour :

Service de maladies infectieuses & tropicales (MIT)
Hospitalisation : ordinaire H732 / confinement H731
Flotte : médecin 06703763.2 / infirmier 0637480096
E-mail : mit.hmim5@gmail.com
Centre de virologie, des maladies infectieuses et tropicales
Hôpital militaire d'instruction M^ed V de Rabat

Figure 3: *Data Intake form (2nd page).*

Table 3: *Population characteristics.*

Characteristics	Value N=186 (%)
Age in years#	34 [27-46.25]
Age < 40 years°	
No	70 (37.6)
Yes	116 (62.4)
Gender°	
M	169 (90.9)
F	17 (9.1)
Comorbidities°	
No	166 (89.2)
yes	20 (10.8)
Time to diagnosis < 5 days°	
No	47 (25.3)
Yes	139 (74.7)
Clinical presentation°	
Asymptomatic	84 (45.2)
Symptomatic	102 (54.8)
Lung involvement on CT scan°	
Normal	99 (53.2)
Minimal	44 (23.7)
Moderate	29(15.6)
Extensive	11 (5.9)
Severe	3 (1.6)
Critical	0
Normal CRP level °	
No	34 (18.3)
Yes	152 (81.7)
Normal LDH level°	
No	46 (24.7)
Yes	140 (75.3)
Normal ferritin°	
No	25 (13.4)
Yes	161 (86.6)
Lymphopenia°	
Yes	62 (33.3)
No	124 (66.7)
Severity score NEWS°	
Asymptomatic	84 (45.2)
Mild form	35 (18.8)
Moderate form	62 (33.3)
Severe form	5 (2.7)
Critical form	0
Negative PCR on D6 D8°	
No	135 (72.6)
Yes	51(27.4)

Table 4: *number and rate of cases according to the age of the patients.*

Age (in years)		Frequency	Percentage
Valide	18	3	1,6
	19	3	1,6
	20	2	1,1
	22	4	2,2
	23	11	5,9
	24	8	4,3
	25	7	3,8
	26	5	2,7
	27	9	4,8
	28	9	4,8
	29	2	1,1
	30	7	3,8
	31	7	3,8
	32	4	2,2
	33	10	5,4
	34	4	2,2
	35	5	2,7
	36	5	2,7
	37	4	2,2
	38	2	1,1
	39	4	2,2
	40	5	2,7
	41	3	1,6
	43	6	3,2
	44	4	2,2
	45	2	1,1
	46	5	2,7
	47	5	2,7
	48	11	5,9
	49	6	3,2
	50	5	2,7
	51	2	1,1
	52	1	,5
	53	2	1,1
	54	2	1,1
	55	2	1,1
	56	1	,5
	57	1	,5
	58	3	1,6
	59	1	,5
	61	2	1,1
	67	1	,5
	72	1	,5
	Total	186	100,0

Table 5: *number and rate of cases according to the gender of the patients.*

Gender		Frequency	Percentage
Valide	Female	17	9,1
	Male	169	90,9
	Total	186	100,0

Table 6: *number and rate of cases according to the presence of comorbidities.*

Comorbidities		Frequency	Percentage
Valide	oui	20	10,8
	non	166	89,2
	Total	186	100,0

Table 7: *number and rate of cases according to diagnosis delay.*

Diagnosis delay (in days)		Frequency	Percentage
Valide	1	3	1,6
	2	27	14,5
	3	15	8,1
	4	9	4,8
	5	9	4,8
	6	8	4,3
	7	14	7,5
	8	4	2,2
	9	5	2,7
	10	4	2,2
	11	1	,5
	15	1	,5
	19	1	,5
	30	1	,5
	Total	102	54,8
Manquant	Système	84	45,2
Total		186	100,0

Table 8: *number and rate of cases according to the extent of lesions on CT scan.*

Extent of lesions on CT scan		Frequency	Percentage
Valide	Normale	99	53,2
	Minime	44	23,7
	Modérée	29	15,6
	Sévère	3	1,6
	Etendue	11	5,9
	Total	186	100,0

A

YAUME DU MAROC

Ministère de la Santé

—

Le Ministre

Circulaire N°: 022....

المملكة المغربية

وزارة الصحة

الوزير

Royaume du Maroc Div.com Ministère de la Santé

23 MARS 2020

MINISTERE DE LA SANTE
Arrivée
Date : 24/03/20
N° : 63

Messieurs les Directeurs des Centres Hospitaliers Universitaires
Mesdames et Messieurs les Directeurs Régionaux de la Santé

Objet : Prescription et dispensation de la CHLOROQUINE et de l'HYDROXYCHLOROQUINE au niveau des établissements de soins.

Suite à la pandémie Mondiale du SARS-CoV-2 (COVID-19), le Ministère de la Santé a décidé en concertation avec le **comité technique et scientifique du programme national de prévention et du contrôle de la grippe et des Infections Respiratoires Aigües Sévères**, l'introduction de la CHLOROQUINE et de l'HYDROXYCHLOROQUINE dans la prise en charge thérapeutique des cas confirmés Covid-19.

Les recommandations dudit comité ont pour objet de fournir aux professionnels de la santé les éléments essentiels dans la prise en charge des cas confirmés Covid-19 **(Annexe 1)**.

À cet effet, des efforts considérables consentis par notre département ont été élaborés afin d'assurer la disponibilité de ces médicaments.

Conscient de l'importance de cette prise en charge et afin de garantir une gestion rationnelle de ces produits, il s'avère important de veiller au respect des différents aspects relatifs à sa gestion de stocks des médicaments spécial COVID-19, notamment :

- Les stocks en CHLOROQUINE et d'HYDROXYCHLOROQUINE doivent être gérés par les responsables des Unités Régionales d'Approvisionnement et de la Pharmacie au niveau des Directions Régionales de la Santé dans un local sécurisé, tout en élaborant une liste de délivrance nominative par classe thérapeutique adressée aux structures de prise en charge ;
- Toute prescription doit être réalisée sur une ordonnance nominative **(Modèle en Annexe 2)** accompagnée des informations nécessaires conditionnant la délivrance de ces médicaments ;
- Toutes les précautions doivent être prises pour le respect du circuit d'approvisionnement afin de garantir la sécurité d'utilisation de ces médicaments. En parallèle, le processus de prescription, de dispensation et d'administration doit faire l'objet d'un suivi spécifique et régulier pour s'assurer de la destination effective de ces médicaments aux patients. Pour ce faire, la traçabilité devrait être assurée par la mise en place d'un registre de gestion et de dispensation.
- Une attention particulière devra être apportée à l'utilisation de ces médicaments pour d'autres pathologies que le COVID-19. Pour cela, l'instauration d'un support d'information doit permettre un suivi rigoureux de cette utilisation. Pour ce faire, la traçabilité devrait être assurée par la mise en place d'un support de gestion et de dispensation spécifique dédié à ces médicaments entre les structures de soins.

335 شارع محمد الخامس - الرباط - الهاتف : 21 11 76 537 212 + - الفاكس : 95 38 76 537 212 +
335, Avenue Mohammed V Rabat - Tél : +212 537 76 11 21 - Fax : +212 537 76 38 95 - www.sante.gov.ma

B

- Tenir informés la Division de l'Approvisionnement, de façon régulière, des éventuelles besoins en ces produits au niveau des structures de prise en charge des patients ;
- Les ordonnances nominatives doivent être faxées à la Division de l'Approvisionnement au *N°: +212 5 37 69 59 18 /16* et la Direction du Médicament et de la Pharmacie au *N°: + 212 5 37 68 19 31* afin d'assurer les stocks de sécurité et un approvisionnement régulier.

Aussi, il vous appartient de prendre toutes les mesures nécessaires en vue de doter les structures de prise en charge relevant de votre région des moyens nécessaires pour garantir un approvisionnement régulier et une gestion rationnelle de ces médicaments.

J'attache un intérêt particulier quant au respect et à l'application stricte des termes de la présente circulaire qui doit faire l'objet d'une large diffusion auprès de vos structures.

Ministre de la Santé

Khalid AIT TALEB

Ampliations :

- Monsieur le Secrétaire Général ;
- Monsieur l'Inspecteur Général ;
- Monsieur le Chef de Cabinet ;
- Madame et Messieurs les Directeurs de l'Administration Centrale ;
- Madame et Mesieurs les Chefs des Divisions rattachées au Secrétariat Général.

355, Av.Mohammed V, Rabat. / Tél :0537761121. Fax : 0537768401 / www.sante.gov.ma

C

ANNEXE 1

Recommandations de prise en charge des infections à coronavirus de COVID-19

1. **Protocoles thérapeutiques :**

   - **Traitement de première intention :**

   Chloroquine (Nivaquine) 500 mg X 2/j, pendant 10 jours **Ou** Sulfate d'hydroxy-chloroquine
   (Plaquinine) 200 mg X 3/j pendant 10 jours
   En association avec l'Azithromycine: 500 mg à J1, puis 250 mg /jour de J2 à J7.

   - **Traitement de deuxième intention :**

   L'association Lopinavir/Ritonavir: 400mg X 2 par jour pendant 10 jours.

   - **Antibiothérapie :** Non systématique, indiquée si surinfection bactérienne.

   Amoxicilline + acide clavulanique, 3g par jour,
   Ou Moxifloxacine 400mg/j en une seule,
   Ou Levofloxacione 500 mg/j en une seule prise.

   - **Nébulisation**: à utiliser si besoin, avec les précautions nécessaires en matière de prévention des infections liées aux soins.

   - **Héparine à bas poids moléculaire** : Si alitement.

2. **Bilan à réaliser pour les patients en dehors de la réanimation**

   - Bilan minimal à l'admission : NFS, CRP, Glycémie, urée, créatininémie, transaminases, ECG, Radiographie thoracique ;
   - Les cas bénins ou modérés doivent bénéficier d'une surveillance médicale biquotidienne ;
     et obligatoire pour détecter précocement tout signe d'aggravation.
   - Les éléments de surveillance doivent être obligatoirement notifiés sur le dossier patient.

3. **Critères de transfert en réanimation des cas initialement bénins ou modérés : devant la présence d'un seul des critères suivants :**

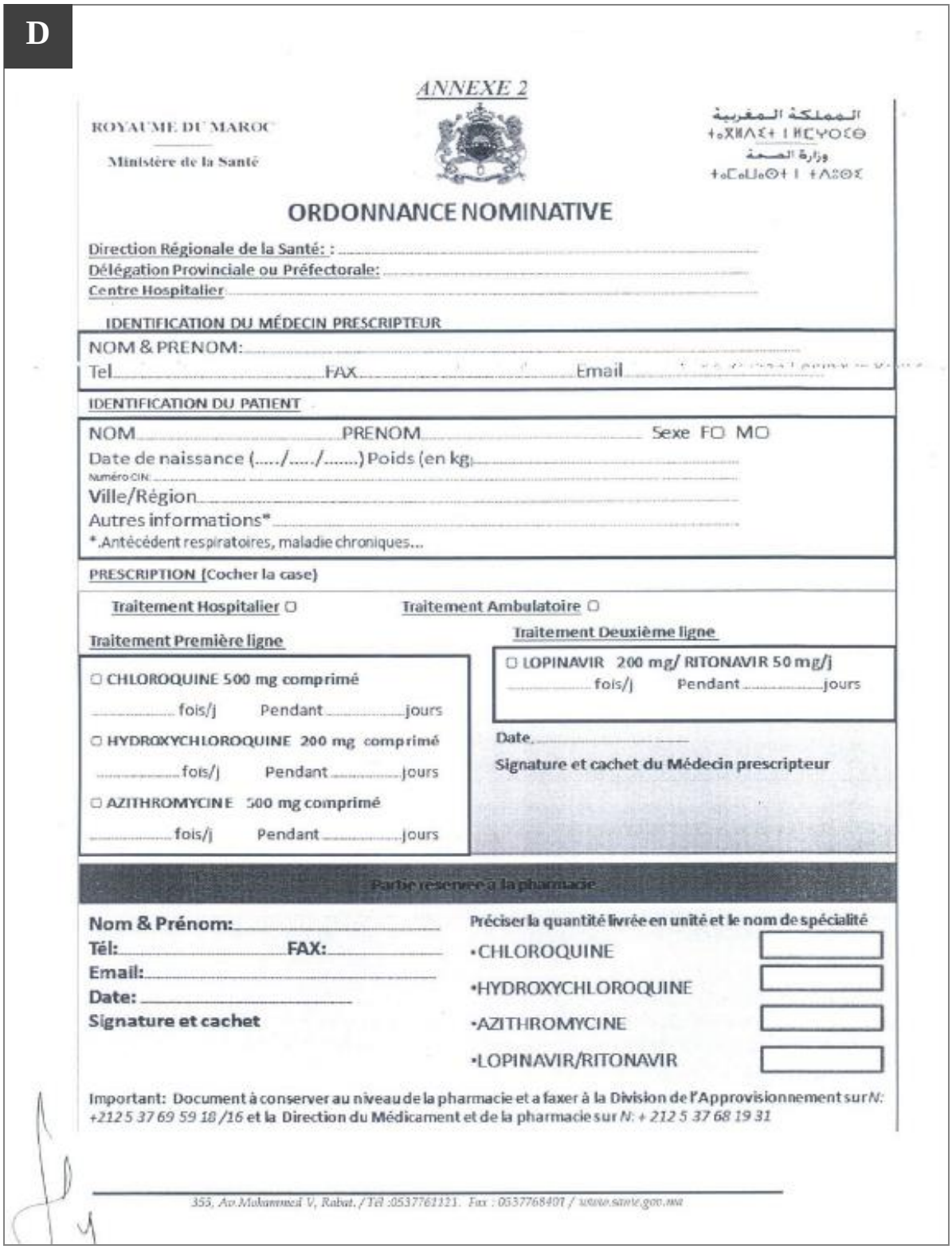
   - Troubles neurologiques: troubles de la conscience ;
   - Polypnée: FR> ou égale à 30 cycles par min ;
   - TA systolique <90 mm-Hg ;
   - Fréquence cardiaque: >120 bat/min ;
   - Saturation en oxygène <92 % sous 4l/min d'O2.

NB : Nécessité de chariot de déchoquage avec traitement et équipement nécessaires. Le protocole thérapeutique des cas de COVID-19 en réanimation sera précisé ultérieurement au sein d'un sous-groupe de réanimateurs.

4. **Tests de diagnostic rapide :** Le comité recommande la mise à disposition des tests rapides antigéniques pour rendre plus facile et plus rapide la confirmation du diagnostic.

355, Av.Mohammed V, Rabat. / Tél :0537761121. Fax : 0537768401 / www.sante.gov.ma

D



ANNEXE 2

ROYAUME DU MAROC

Ministère de la Santé

المملكة المغربية

وزارة الصحة

ORDONNANCE NOMINATIVE

Direction Régionale de la Santé: :

Délégation Provinciale ou Préfectorale:

Centre Hospitalier

IDENTIFICATION DU MÉDECIN PRESCRIPTEUR

NOM & PRENOM:

Tel FAX Email

IDENTIFICATION DU PATIENT

NOM PRENOM Sexe FO MO

Date de naissance (...../...../.....) Poids (en kg)

Numéro CIN:

Ville/Région

Autres informations*

*.Antécédent respiratoires, maladie chroniques...

PRESCRIPTION (Cocher la case)

Traitement Hospitalier ☐ Traitement Ambulatoire ☐

Traitement Première ligne

☐ CHLOROQUINE 500 mg comprimé

..... fois/j Pendant ..... jours

☐ HYDROXYCHLOROQUINE 200 mg comprimé

..... fois/j Pendant ..... jours

☐ AZITHROMYCINE 500 mg comprimé

..... fois/j Pendant ..... jours

Traitement Deuxième ligne

☐ LOPINAVIR 200 mg/ RITONAVIR 50 mg/j

..... fois/j Pendant ..... jours

Date

Signature et cachet du Médecin prescripteur

Partie reservée à la pharmacie

Nom & Prénom:

Tél: FAX:

Email:

Date:

Signature et cachet

Préciser la quantité livrée en unité et le nom de spécialité

- CHLOROQUINE
- HYDROXYCHLOROQUINE
- AZITHROMYCINE
- LOPINAVIR/RITONAVIR

Important: Document à conserver au niveau de la pharmacie et a faxer à la Division de l'Approvisionnement sur N: +212 5 37 69 59 18 /16 et la Direction du Médicament et de la pharmacie sur N: + 212 5 37 68 19 31

355, Av.Mohammed V, Rabat. / Tél :0537761121. Fax : 0537768407 / www.sante.gov.ma

Figure 4: ***(A, B, C, D)*** *National protocol for the management and treatment of COVID-19 (March 23d, 2020)* **[112]**.

Table 9: *number and rate of cases according to the NEWS Severity score.*

NEWS Severity score		Frequency	Percentage
Valide	Asymptomatique	84	45,2
	Bénin	35	18,8
	Modéré	62	33,3
	Sévère	5	2,7
	Total	186	100,0

Table 10: *number and rate of cases according to negativity of PCR on days 6th and 8th.*

Negative PCR on days 6th and 8th		Frequency	Percentage
Valide	oui	51	27,4
	non	135	72,6
	Total	186	100,0

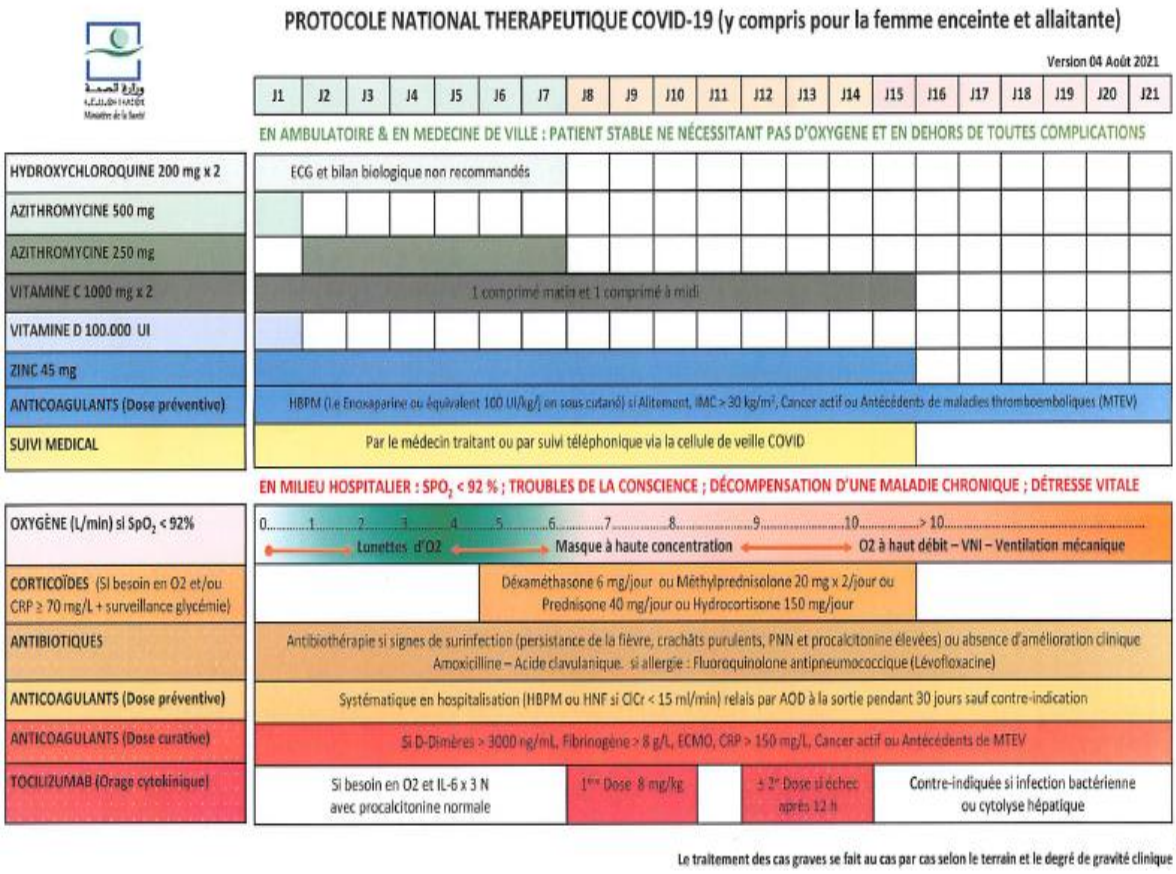
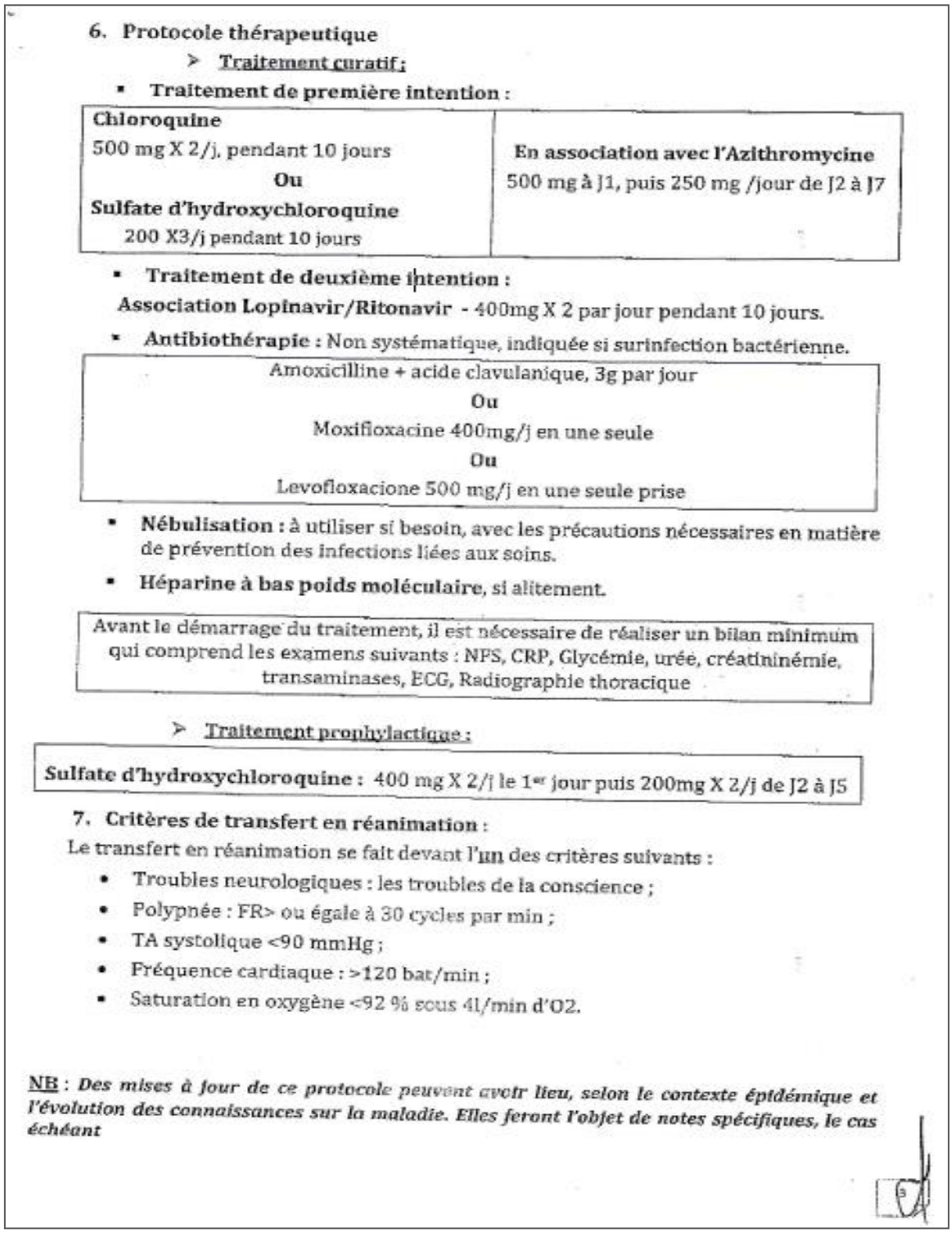


Figure 5: *National protocol for the management and treatment of COVID-19 (update of August 4th, 2021)* **[112]**.



6. **Protocole thérapeutique**

➢ **Traitement curatif :**

▪ **Traitement de première intention :**

Chloroquine 500 mg X 2/j, pendant 10 jours **Ou** **Sulfate d'hydroxychloroquine** 200 X3/j pendant 10 jours	**En association avec l'Azithromycine** 500 mg à J1, puis 250 mg /jour de J2 à J7

▪ **Traitement de deuxième intention :**

Association Lopinavir/Ritonavir - 400mg X 2 par jour pendant 10 jours.

▪ **Antibiothérapie :** Non systématique, indiquée si surinfection bactérienne.

Amoxicilline + acide clavulanique, 3g par jour
Ou
Moxifloxacine 400mg/j en une seule
Ou
Levofloxacione 500 mg/j en une seule prise

▪ **Nébulisation :** à utiliser si besoin, avec les précautions nécessaires en matière de prévention des infections liées aux soins.

▪ **Héparine à bas poids moléculaire**, si alitement.

Avant le démarrage du traitement, il est nécessaire de réaliser un bilan minimum qui comprend les examens suivants : NFS, CRP, Glycémie, urée, créatininémie, transaminases, ECG, Radiographie thoracique

➢ **Traitement prophylactique :**

Sulfate d'hydroxychloroquine : 400 mg X 2/j le 1er jour puis 200mg X 2/j de J2 à J5

7. **Critères de transfert en réanimation :**

Le transfert en réanimation se fait devant l'un des critères suivants :

- Troubles neurologiques : les troubles de la conscience ;
- Polypnée : FR> ou égale à 30 cycles par min ;
- TA systolique <90 mmHg ;
- Préquence cardiaque : >120 bat/min ;
- Saturation en oxygène <92 % sous 4l/min d'O2.

NB : ***Des mises à jour de ce protocole peuvent avoir lieu, selon le contexte épidémique et l'évolution des connaissances sur la maladie. Elles feront l'objet de notes spécifiques, le cas échéant***

Figure 6: *National protocol for the management and treatment of COVID-19 (update of April 7th, 2020)* **[112]**.

Table 11: *factors associated with asymptomatic condition in univariate analysis.*

	Univariate analysis		
	OR	IC 95%	P
Age < 40 years			
No	1		
Yes	1.036	0.571-1.881	0.906
Gender			
M	1		
F	0.636	0.225-1.800	0.394
Comorbidities			
No	1		
Yes	2.068	0.758-5.643	0.156
Time to diagnosis < 5 days			
No	1		
Yes	0.0001	-	0.997
Normal CT scan			
No	1		
Yes	0.248	0.133-0.460	0.0001
Normal CRP level			
No	1		
Yes	4.919	1.927-12.559	0.001
Normal LDH level			
No	1		
Yes	0.565	0.283-1.127	0.105
Normal ferritinemia			
No	1		
Yes	0.135	0.39-0.468	0.002
Lymphopenia			
Yes	1		
No	2.016	1.071-3.797	0.030
Early virologic clearance			
No	1		
Yes	0.650	0.340-1.241	0.191

Table 12: *factors associated with normal CT scan features in univariate analysis.*

	Univariate analysis		
	OR	IC 95%	P
Age < 40 years			
No	1		
Yes	0.315	0.170-0.585	0.0001
Gender			
M	1		
F	0.988	0.364-2.682	0.980
Asymptomatic			
No	1		
Yes	4.038	2.174-7.502	0.0001
Comorbidities			
No	1		
Yes	1.820	0.707-4.684	0.214
Time to diagnosis < 5 days			
No	1		
Yes	0.444	0.226-0.875	0.019
Normal CRP level			
No	1		
Yes	17.714	5.178-60.608	0.0001
Normal LDH level			
No	1		
Yes	0.366	0.183-0.733	0.005
Normal ferritinemia			
No	1		
Yes	0.0001	-	0.998
Lymphopenia			
Yes	1		
No	5.168	2.643-10.105	0.0001
Early virologic clearance			
No			
Yes	0.522	0.268-1.016	0.056

Table 13: *factors associated with asymptomatic condition in multivariate analysis.*

	Multivariate analysis		
	OR	IC 95%	P
Comorbidities			
No	1		
Yes	1.526	0.509-4.572	0.450
Normal CT scan			
No	1		
Yes	2.584	1.272-5.252	0.009
Normal CRP level			
No	1		
Yes	2.145	0.710-6.481	0.176
Normal LDH level			
No	1		
Yes	1.018	0.451-2.297	0.966
Normal ferritinemia			
No	1		
Yes	0.389	0.094-1.613	0.193
Lymphopenia			
Yes	1		
No	0.982	0.467-2.066	0.962
Early virologic clearance			
No	1		
Yes	0.774	0.378-1.585	0.484

Table 14: *factors associated with normal CT scan features in multivariate analysis.*

	Multivariate analysis		
	OR	IC 95%	P
Age < 40 years			
No	1		
Yes	0.318	0.145-0.699	0.004
Asymptomatic			
No	1		
Yes	3.896	1.667-9.102	0.002
Time to diagnosis < 5 days			
No	1		
Yes	1.509	0.572-3.982	0.406
Normal CRP level			
No	1		
Yes	10.079	2.493-40.746	0.001
Normal LDH level			
No	1		
Yes	0.549	0.226-1.333	0.185
Lymphopenia			
Yes	1		
No	2.830	1.282-6.249	0.010
Early virologic clearance			
No	1		
Yes	0.412	0.175-0.971	0.043

References

[1] Yang W, Sirajuddin A, Zhang X, *et al*. The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Eur Radiol. 2020; 30(9): 4874-4882.

[2] 1Wang C, Wang Z, Wang G, Lau JY, Zhang K, Li W. COVID-19 in early 2021: current status and looking forward. Signal Transduct Target Ther. 2021; 6(1): 114.

[3] https://covid19.who.int/

[4] Kasraoui S. Coronavirus Pandemic: A Timeline of COVID-19 in Morocco. Morocco World News. 2020.

[5] https://www.worldometers.info/coronavirus/

[6] Payne S. Family Coronaviridae, Viruses, Academic Press. 2017; Chapter 17: 149-158.

[7] Souilmi *et al.* An ancient viral epidemic involving host coronavirus interacting genes more than 20,000 years ago in East Asia 2021. Current Biology. 2021; 31: 3504-3514.

[8] Qu J, Wickramasinghe C. SARS, MERS and the sunspot cycle. Current science. 2017; vol. 113, n° 8.

[9] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nature Rev Microbiol. 2016; 14(8): 523-534.

[10] da Costa VG, Moreli ML, Saivish MV. The emergence of SARS, MERS and novel SARS-2 coronaviruses in the 21st century. Arch Virol. 2020; 165: 1517-1526.

[11] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020; 324(8): 782-793.

[12] Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181(2): 271-280.

[13] Sungnak W, Huang N, Bécavin C, *et al.*HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020; 26(5): 681-687.

[14] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptorACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoVinfection. Front Med. 2020; 14(2): 185-192.

[15] Mancia G, Rea F, Ludergnani M, Apolone G,Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med. 2020; 382(25): 2431-2440.

[16] Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, *et al*. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. JAMA. 2020; 324(2): 168-177.

[17] Xu Z, Shi L,Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8(4): 420-422.

[18] van de Veerdonk FL, Netea MG, van Deuren M, *et al*. Kallikrein kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife. 2020; 9: e57555.

[19] Tang N, Li D,Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.

[20] Thachil J, Tang N, Gando S, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020; 18(5):1023-1026.

[21] Klok FA, Kruip MJHA, van der Meer NJM, *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191: 145-147.

[22] Zhang YZ, Holmes EC. A genomic perspective on the origin and emergence of SARS-CoV-2. Cell. 2020; 181(2): 223-227.

[23] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B Huang CL, *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270–273.

[24] Hu B, Zeng LP, Yang XL, Ge, XY, Zhang W, Li B, Xie JZ, Shen XR, Zhang YZ, Wang N, *et al*. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS. 2017; Pathog.13, e1006698.

[25] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat. Rev. Microbiol. 2019; 17: 181-192.

[26] Lin XD, Wang W, Hao ZY, Wang ZX, Guo WP, Guan XQ, Wang MR, Wang HW, Zhou RH, Li MH, *et al*. Extensive diversity of coronaviruses in bats from China. Virology. 2017; 507: 1-10.

[27] Sabir JSM, Lam TTY, Ahmed MMA, Li L, Shen Y, Abo-Aba SEM, Qureshi MI, Abu-Zeid M, Zhang Y, Khiyami MA, *et al*. Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia. Science. 2016; 351: 81-84.

[28] Hossain MG, Javed A, Akter S, Saha S. SARS-CoV-2 host diversity: An update of natural infections and experimental evidence. J Microbiol Immunol Infect. 2021; 54(2): 175-181.

[29] Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021; 174(1): 69-79.

[30] Wei J, Li Y. Airborne spread of infectious agents in the indoor environment. Am J Infect Control. 2016; 44: S102-108.

[31] Klompas M, Baker MA, Rhee C. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. JAMA. 2020; 324: 441-442.

[32] Fennelly KP. Particle sizes of infectious aerosols: implications for infection control. Lancet Respir Med. 2020; 8:914-924.

[33] Lu J, Gu J, Li K, *et al*. COVID-19 outbreak associated with air conditioning in restaurant, Guangzhou, China, 2020. Emerg Infect Dis. 2020; 26: 1628-1631.

[34] Santarpia JL, Herrera VL, Rivera DN, *et al*. The infectious nature of patient-generated SARS-CoV-2 aerosol. medRxiv. 2020; 20041632.

[35] Lednicky JA, Lauzard M, Fan ZH, *et al*. Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. Int J Infect Dis. 2020; 100: 476-482.

[36] Ma J, Qi X, Chen H, *et al*. COVID-19 patients in earlier stages exhaled millions of SARS-CoV-2 per hour. Clin Infect Dis. 2021; 72(10): e652-654.

[37] Courtemanche C, Garuccio J, Le A, *et al*. Strong social distancing measures in the United States reduced the COVID-19 growth rate. Health Aff (Millwood). 2020; 39:1237-1246.

[38] Chu DK, Akl EA, Duda S, *et al*. COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet. 2020; 395: 1973-1987.

[39] Hu M, Lin H, Wang J, *et al*. The risk of COVID-19 transmission in train passengers: an epidemiological and modelling study. Clin Infect Dis. 2021; 72(4): 604-610.

[40] James A, Eagle L, Phillips C, *et al*. High COVID-19 attack rate among attendees at events at a church - Arkansas, March 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 632-635.

[41] Adam DC, Wu P, Wong JY, *et al*. Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. Nat Med. 2020; 26(11): 1714-1719.

[42] Furuse Y, Sando E, Tsuchiya N, *et al*. Clusters of Coronavirus Disease in communities, Japan, January-April 2020. Emerg Infect Dis. 2020; 26(9): 2176-2179.

[43] Qian H, Miao T, Liu L, *et al*. Indoor transmission of SARS-CoV-2. Indoor Air. 2021; 31(3): 639-645.

[44] Nishiura H, Oshitani H, Kobayashi T, *et al*. Closed environments facilitate secondary transmission of coronavirus disease 2019 (COVID-19). medRxiv. 2020; 20029272.

[45] Leclerc QJ, Fuller NM, Knight LE, *et al.* CMMID COVID-19 Working Group. What settings have been linked to SARS-CoV-2 transmission clusters? Wellcome Open Res. 2020; 5: 83.

[46] Cai J, Sun W, Huang J, *et al*. Indirect virus transmission in cluster of COVID-19 cases, Wenzhou, China, 2020. Emerg Infect Dis. 2020; 26: 1343-1345.

[47] Wang Y, Tian H, Zhang L, *et al*. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. BMJ Glob Health. 2020; 5(5): e002794.

[48] Ran L, Chen X, Wang Y, *et* al. Risk factors of healthcare workers with corona virus disease 2019: a retrospective cohort study in a designated hospital of Wuhan in China. Clin Infect Dis. 2020; 1(16):2218-2221.

[49] van Kampen JJA, van de Vijver DAMC, Fraaij PLA, *et al*. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. medRxiv.2020; 20125310.

[50] Cheng HY, Jian SW, Liu DP, *et al*. Taiwan COVID-19 Outbreak Investigation Team. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA Intern Med. 2020; 180(9): 1264.

[51] Shi J, Wen Z, Zhong G, *et al*. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science. 2020; 368: 1016-1020.

[52] Sit THC, Brackman CJ, Ip SM, *et al*. Infection of dogs with SARS-CoV-2. Nature. 2020; 586: 776-778.

[53] Richard M, Kok A, de Meulder D, *et al*. SARS-CoV-2 is transmitted via contact and via the air between ferrets. Nat Commun. 2020; 11: 3496.

[54] Garigliany M, Van Laere AS, Clercx C, *et al*. SARS-CoV-2 natural transmission from human to cat, Belgium, March 2020. Emerg Infect Dis. 2020; 26(12): 3069-3071.

[55] Halfmann PJ, Hatta M, Chiba S, *et al*. Transmission of SARS-CoV-2 in domestic cats [Letter]. N Engl J Med. 2020; 383:592-594.

[56] Oreshkova N, Molenaar RJ, Vreman S, *et al*. SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. Euro Surveill. 2020; 25(23): 2001005.

[57] Oude Munnink BB, Sikkema RS, Nieuwenhuijse DF, *et al*. Jumping back and forth: anthropozoonotic and zoonotic transmission of SARS-CoV-2 on mink farms. bioRxiv. 2020; 277152.

[58] Yang Z, Liu Y. Vertical transmission of severe acute respiratory syndrome coronavirus 2: A systematic review. Am J Perinatol. 2020; 37: 1055-1060.

[59] Zeng H, Xu C, Fan J, *et al*. Antibodies in infants born to mothers with COVID-19 pneumonia. JAMA. 2020; 323(18): 1848-1849.

[60] Dong L, Tian J, He S, *et al*. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020; 323(18): 1846-1848.

[61] Kimberlin DW, Stagno S. Can SARS-CoV-2 infection be acquired in utero? More definitive evidence is needed. JAMA. 2020; 323(18):1788-1789.

[62] Zeng L, Xia S, Yuan W, *et al*. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr. 2020; 174(7): 722-725.

[63] Alzamora MC, Paredes T, Caceres D, *et al*. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol.2020; 37: 861-865.

[64] Patané L, Morotti D, Giunta MR, *et al*. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019-positive mothers and neonates at birth. Am J Obstet Gynecol MFM. 2020; 2: 100145.

[65] Baud D, Greub G, Favre G, *et al*. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. JAMA. 2020; 323(21): 2198-2200.

[66] Vivanti AJ, Vauloup-Fellous C, Prevot S, *et al*. Transplacental transmission of SARS-CoV-2 infection. Nat Commun. 2020; 11: 3572.

[67] Alamar I, Abu-Arja MH, Heyman T, *et al*. A possible case of vertical transmission of SARS-CoV-2 in a newborn with positive placental in situ hybridization of SARS-CoV-2 RNA. J Pediatric Infect Dis Soc. 2020; 9(5): 636-639.

[68] Groß R, Conzelmann C, Müller JA, *et al*. Detection of SARS-CoV-2 in human breastmilk [Letter]. Lancet. 2020; 395: 1757-1758.

[69] Marin Gabriel MA, Cuadrado I, Alvarez Fernandez B, *et al*. Neo-COVID-19 Research Group. Multicentre Spanish study found no incidences of viral transmission in infants born to mothers with COVID-19. Acta Paediatr. 2020; 109(11): 2302-2308.

[70] Chambers C, Krogstad P, Bertrand K, *et al*. Evaluation for SARS-CoV-2 in breast milk from 18 infected women. JAMA. 2020; 324(13): 1347-1348.

[71] Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission [Editorial]. Gastroenterology. 2020; 158: 1518-1519.

[72] Deng W, Bao L, Gao H, *et al*. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in Rhesus macaques. bioRxiv. 2020; 11(1): 4400.

[73] Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020; 323(18): 1843-1844.

[74] Kim JM, Kim HM, Lee EJ, *et al*. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. Osong Public Health Res Perspect. 2020; 11: 112-117.

[75] Sun J, Xiao J, Sun R, *et al*. Prolonged persistence of SARS-CoV-2 RNA in body fluids. Emerg Infect Dis. 2020; 26: 1834-1838.

[76] Parasa S, Desai M, Thoguluva Chandrasekar V, *et al*. Prevalence of gastrointestinal symptoms and fecal viral shedding in patients with coronavirus disease 2019: a systematic review and meta-analysis. JAMA Netw Open. 2020; 3: e2011335.

[77] van Doorn AS, Meijer B, Frampton CMA, *et al*. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for fecal-oral transmission. Aliment Pharmacol Ther. 2020; 52(8): 1276-1288.

[78] Patel J. Viability of SARS-CoV-2 in fecal bio-aerosols [Letter]. Colorectal Dis. 2020; 22(9): 1022.

[79] Lai CKC, Ng RWY, Wong MCS, *et al*. Epidemiological characteristics of the first 100 cases of coronavirus disease 2019 (COVID-19) in Hong Kong Special Administrative Region, China, a city with a stringent containment policy. Int J Epidemiol. 2020; 49(4): 1096-1105.

[80] Liu Y, Ning Z, Chen Y, *et al.* Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature. 2020; 582: 557-560.

[81] Kang M, Wei J, Yuan J, *et al.* Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. Ann Intern Med. 2020; 173(12): 974-980.

[82] Li D, Jin M, Bao P, *et al.* Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA Netw Open. 2020; 3: e208292.

[83] Qiu L, Liu X, Xiao M, *et al.* SARS-CoV-2 is not detectable in the vaginal fluid of women with severe COVID-19 infection. Clin Infect Dis. 2020; 71: 813-817.

[84] Scorzolini L, Corpolongo A, Castilletti C, *et al*. Comment of the potential risks of sexual and vertical transmission of Covid-19 infection. Clin Infect Dis. 2020; 71(16): 2298.

[85] Hogan CA, Stevens BA, Sahoo MK, *et al*. High frequency of SARS-CoV-2 RNAemia and association with severe disease. Clin Infect Dis. 2021; 72(9): e291-e295.

[86] Fajnzylber JM, Regan J, Coxen K, *et al*. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun. 2020; 11(1): 5493.

[87] Chang L, Zhao L, Gong H, *et al*. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis. 2020; 26: 1631-1633.

[88] Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181: 271-280.e8.

[89] Walls AC, Park YJ, Tortorici MA, *et al*. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020; 181: 281-292.e6.

[90] Wölfel R, Corman VM, Guggemos W, *et al*. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020; 581: 465-469.

[91] Jing QL, Liu MJ, Zhang ZB, *et al*. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. Lancet Infect Dis. 2020; 20(10): 1141-1150.

[92] Rosenberg ES, Dufort EM, Blog DS, *et al*. New York State Coronavirus 2019 Response Team. COVID-19 testing, epidemic features, hospital outcomes, and household prevalence, New York State - March 2020. Clin Infect Dis. 2020; 71(8): 1953-1959.

[93] Zhang J, Litvinova M, Liang Y, *et al*. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. Science. 2020; 368: 1481-1486.

[94] Davies NG, Klepac P, Liu Y, *et al*. CMMID COVID-19 working group. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020; 26:1205-1211.

[95] Gudbjartsson DF, Helgason A, Jonsson H, *et al*. Spread of SARS-CoV-2 in the Icelandic population. N Engl J Med. 2020; 382: 2302-2315.

[96] Li W, Zhang B, Lu J, *et al*. The characteristics of household transmission of COVID-19. Clin Infect Dis. 2020; 71(8): 1943-1946.

[97] Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. JAMA. 2020; 323(23): 2427-2429.

[98] Yonker LM, Neilan AM, Bartsch Y, *et al*. Pediatric SARS-CoV-2: clinical presentation, infectivity, and immune responses. J Pediatr. 2020; 227: 45-52.e5.

[99] L'Huillier AG, Torriani G, Pigny F, *et al*. Culture-competent SARS-CoV-2 in nasopharynx of symptomatic neonates, children, and adolescents. Emerg Infect Dis. 2020; 26(10): 2494-2497.

[100] Heald-Sargent T, Muller WJ, Zheng X, *et al*. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr. 2020; 174(9): 902-903.

[101] Maltezou HC, Vorou R, Papadima K, *et al*. Transmission dynamics of SARS-CoV-2 within families with children in Greece: a study of 23 clusters. J Med Virol. 2020; 93(3): 1414-1420.

[102] Posfay-Barbe KM, Wagner N, Gauthey M, *et al*. COVID-19 in children and the dynamics of infection in families. Pediatrics. 2020; 146(2): e20201576.

[103] Park YJ, Choe YJ, Park O, *et al*. COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Contact tracing during coronavirus disease outbreak, South Korea, 2020. Emerg Infect Dis. 2020; 26(10): 2465-2468.

[104] Kim J, Choe YJ, Lee J, *et al*. Role of children in household transmission of COVID-19. Arch Dis Child. 2020; 0: 1-3.

[105] Lewis NM, Chu VT, Ye D, *et al*. Household transmission of SARS-CoV 2 in the United States. Clin Infect Dis. 2021; 73(7): 1805-1813.

[106] Korber B, Fischer WM, Gnanakaran S, *et al.* Sheffield COVID-19 Genomics Group. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell. 2020; 182: 812-827.e19.

[107] Volz EM, Hill V, McCrone JT, *et al*. Evaluating the effects of SARS-CoV-2 Spike mutation D614G on transmissibility and pathogenicity. Cell. 2021; 184(1): 64-75.e11.

[108] Daniloski Z, Guo X, Sanjana NE. The D614G mutation in SARS-CoV-2 Spike increases transduction of multiple human cell types. bioRxiv. 2020; 7: 151357.

[109] Zhang L, Jackson CB, Mou H, *et al*. The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity. bioRxiv. 2020; 148726.

[110] Mansbach RA, Chakraborty S, Nguyen K, *et al*. The SARS-CoV-2 Spike variant D614G favors an open conformational state. Sci Adv. 2021; 7(16): eabf3671.

[111] https://labs.letemps.ch/interactive/2020/carte-coronavirus-monde/#world-anchor

[112] Health Ministry website: https://www.sante.gov.ma/Pages/corona.aspx

[113] Gilbert GL. Commentary: SARS, MERS and COVID-19-new threats; old lessons. Int J Epidemiol. 2020; 49(3): 726-728.

[114] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020; 109: 102433.

[115] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, *et al*. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. 2020; 382: 1199-1207.

[116] Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China, J. Med. Virol. 2020; 92(4): 441-447.

[117] Ren LL, Wang LM, Wu ZQ, Xiang ZC, Guo L, Xu T, *et al*. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study, Chinese Med J. 2020; 133(9): 1015-1024

[118] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet. 2020; 395 (10223): 497-506.

[119] Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel Wuhan (2019-nCoV) coronavirus, Am. J. Respir. Crit. Care Med. 2020; 201(4): 7-8.

[120] Lei J, Li J, Li X, Qi X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology. 2020; 295(1): 18.

[121] Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, *et al*. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect. Dis. 2013; 13: 752-761.

[122] Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, *et al*. A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 2003; 348: 1986-1994.

[123] Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, *et al*. Importation and human-to-human transmission of a novel coronavirus in Vietnam, N. Engl. J. Med. 2020; 382(9): 872-874.

[124] Freeman WM, Walker SJ, Vrana KE. Quantitative RT-PCR: pitfalls and potential. BioTechniques. 1999; 26 (1): 112-122, 124-125.

[125] Chung YS, Lee NJ, Woo SH, Kim JM, Kim HM, Jo HJ, Park YE, Han MG. Validation of real-time RT-PCR for detection of SARS-CoV-2 in the early stages of the COVID-19 outbreak in the Republic of Korea. Sci Rep. 2021; 11(1): 14817.

[126] Corman VM, Drosten C. Authors' response: SARS-CoV-2 detection by real-time RT-PCR. Euro Surveill. 2020; 25(21): 2001035.

[127] Chan JF, Yip CC, To KK, *et al*. Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/Hel real-time reverse transcription-PCR assay validated *in vitro* and with clinical specimens. J Clin Microbiol. 2020; 58(5): e00310-20.

[128] LeBlanc JJ, Gubbay JB, Li Y, *et al*. Real-time PCR-based SARS-CoV-2 detection in Canadian laboratories. J Clin Virol. 2020; 128: 104433.

[129] Dharavath B, Yadav N, Desai S, *et al*. A one-step, one-tube real-time RT-PCR based assay with an automated analysis for detection of SARS-CoV-2. Heliyon. 2020; 6(7): e04405.

[130] Zóka A, Bekő G. Distinct changes in the real-time PCR detectability of certain SARS-CoV-2 target sequences. Clin Chim Acta. 2020; 507: 248-249.

[131] Kahn M, Schuierer L, Bartenschlager C, *et al*. Performance of antigen testing for diagnosis of COVID-19: a direct comparison of a lateral flow device to nucleic acid amplification-based tests. BMC Infect Dis. 2021; 21, 798.

[132] Corman VM, Haage VC, Bleicker T, Schmidt ML, Mühlemann B, Zuchowski M, *et al*. Comparison of seven commercial SARS-CoV-2 rapid Point-of-Care Antigen tests. medRxiv. 2020; 11.12.20230292.

[133] Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, *et al*. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2020; 8(8): CD013705.

[134] Martínez Chamorro E, Díez Tascón A, Ibáñez Sanz L, Ossaba Vélez S, Borruel Nacenta S. Radiologic diagnosis of patients with COVID-19. Radiologia (Engl Ed). 2021; 63(1): 56-73.

[135] Wong HYF, Lam HYS, Fong AH-T, Leung ST, Chin TW-Y, Lo CSY, *et al*. Frequency and distribution of chest radiographic findings in patients positive for COVID-19. Radiology. 2020; 296: E72-78.

[136] Manna S, Wruble J, Maron SZ, Toussie D, Voutsinas N, Finkelstein M, *et al*. COVID-19: a multimodality review of radiologic techniques, clinical utility, and imaging features. Radiol Cardio-thorac Imaging. 2020; 2(3): e200210.

[137] Schiaffino S, Tritella S, Cozzi A, Carriero S, Blandi L, Ferraris L, *et al*. Diagnostic performance of chest X-ray for COVID-19 pneumonia during the SARS-CoV-2 pandemic in Lombardy, Italy. J Thorac Imaging. 2020; 35 (4): 105-106.

[138] Rubin GD, Ryerson CJ, Haramati LB, Sverzellati N, Kanne JP, *et al*. The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the fleischner society. Radiology. 2020; 296: 172-180.

[139] Jacobi A, Chung M, Bernheim A, Eber C. Portable chest X-ray in coronavirus disease-19 (COVID-19): a pictorial review. Clin Imaging. 2020; 64: 35-42.

[140] Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, *et al*. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020; 296: E32-40.

[141] Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, *et al*. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. 2020; 296: E115-117.

[142] Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, *et al*. Radiological society of North America expert consensus statement on reporting chest CT findings related to COVID-19. Endorsed by the society of thoracic radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging. 2020; 2: e200152.

[143] Li Y, Xia L. Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management. Am J Roentgenol. 2020; 214(6):1280-1286.

[144] Wan Y-L, Schoepf UJ, Wu CC, Giovagnoli DP, Wu M-T, Hsu H-H, *et al*. Preparedness and best practice in radiology department for COVID-19 and other future pandemics of severe acute respiratory infection. J Thorac Imaging. 2020; 35: 239-245.

[145] Zanardo M, Martini C, Monti CB, Cattaneo F, Ciaralli C, Cornacchione P, *et al*. Management of patients with suspected or confirmed COVID-19, in the radiology department. Radiography (Lond). 2020; 26: 264-268.

[146] Kalra MK, Homayounieh F, Arru C, Holmberg O, Vassileva J. Chest CT practice and protocols for COVID-19 from radiation dose management perspective. Eur Radiol. 2020; 30: 6554-6560.

[147] Tofighi S, Najafi S, Johnston SK, Gholamrezanezhad A. Low-dose CT in COVID-19 outbreak: radiation safety, image wisely, and image gently pledge. Emerg Radiol. 2020; 10: 1-5.

[148] Kang Z, Li X, Zhou S. Recommendation of low-dose CT in the detection and management of COVID-2019. Eur Radiol.2020; 30: 4356-4357.

[149] Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019-2020 epidemic: preparing intensive care units-the experience in Sichun province, China. Intensive Care Med. 2020; 46: 357- 360.

[150] Jaspard M, Sow MS, Juchet S, Dienderé E, Serra B, *et al*. Clinical presentation, outcomes and factors associated with mortality: A prospective study from three COVID-19 referral care centres in West Africa. Int J Infect Dis. 2021; 108: 45-52.

[151] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, *et al*. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020; 323(20): w2052-2059.

[152] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, *et al*. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020; 369: m1985.

[153] Zhou F, Yu T, Du R, Fan G, Liu Y, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054-1062.

[154] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, *et al*. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020; 55(5): 2000547.

[155] Wang B, Li Ruobao Li, Zhong Lu, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY). 2020; 12(7): 6049–57.

[156] Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, *et al*. Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med. 2020; 1–8.

[157] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW *et al*. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020; 323(20): 2052–2059.

[158] Osibogun A, Balogun M, Abayomi A, Idris J, Kuyinu Y, *et al*. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. PLoS One. 2021; 16(3): e0248281.

[159] Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, *et al*. Hospitalization rates and characteristics of patients hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(15): 458-464.

[160] Zhang J, Wang X, Jia X, Li J, Hu K, *et al*. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect. 2020; 26(6): 767-772.

[161] Li X, Li T, Wang H. Treatment and prognosis of COVID-19: Current scenario and prospects (Review). Exp Ther Med. 2021; 21(1): 3.

[162] Zheng J: SARS-CoV-2: An emerging coronavirus that causes a global threat. Int J Biol Sci. 2020; 16: 1678-1685.

[163] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18): 1708-1720.

[164] Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection. Ann Intern Med. 2020; 173: 362-367.

[165] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.

[166] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323: 1061-1069.

[167] Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SEB, *et al*. Coronavirus disease 2019 case surveillance-United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 759-765.

[168] Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020; 183: 71-77.

[169] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA. 2020; 323: 1239-1242.

[170] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020; 369: m1966.

[171] Yin X, Li Q, Hou S, *et al*. Demographic, signs and symptoms, imaging characteristics of 2126 patients with COVID-19 pneumonia in the whole quarantine of Wuhan, China. Clin Imaging. 2021; 77: 169-174.

[172] Wang W, Xu Y, Gao R, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020; 323(18): 1843-1844.

[173] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA. 2020; 323(22): 2249-2251.

[174] Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Ann Intern Med. 2020; 173(4): 262-267.

[175] Williams E, Bond K, Zhang B, Putland M, Williamson DA. Saliva as a non-invasive specimen for detection of SARS-CoV-2. J Clin Microbiol. 2020; 58(8): e00776-20.

[176] Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: Issues affecting the results. Expert Rev Mol Diagn. 2020; 20(5): 453-454.

[177] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, *et al.* Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis. 2020; 34: 101623.

[178] Wu C, Chen X, Cai Y, *et al*. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med.2020; 180(7): 934-943.

[179] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, *et al*: Covid-19 in critically Ill patients in the Seattle region - Case Series. N Engl J Med. 2020; 382(21): 2012-2022.

[180] Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, *et al*. COVID-19 related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020; 120: 998-1000.

[181] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, *et al*: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.

[182] Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for radiologists on COVID-19: an update-Radiology scientific expert panel. Radiology. 2020; 296(2): E113-E114.

[183] Mossa-Basha M, Meltzer CC, Kim DC, Tuite MJ, Kolli KP, Tan BS. Radiology department preparedness for COVID-19: radiology scientific expert panel. Radiology. 2020; 296: E106-112.

[184] Raptis CA, Hammer MM, Short RG, Shah A, Bhalla S, Bierhals AJ, *et al*. Chest CT and coronavirus disease (COVID-19): a critical review of the literature to date. AJR Am J Roentgenol. 2020; 215: 839-842.

[185] Litmanovich DE, Chung M, Kirkbride RR, Kicska G, Kanne JP. Review of chest radiograph findings of COVID-19 pneumonia and suggested reporting language. J Thorac Imaging. 2020; 35(6): 354-360.

[186] Ng Ming-Yen, Elaine Y. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiol Cardiothorac Imaging. 2020; 2: e2000034.

[187] Vancheri SG, Savietto G, Ballati F, Maggi A, Canino C, Bortolotto C, *et al*. Radiographic findings in 240 patients with COVID-19 pneumonia: time-dependence after the onset of symptoms. Eur Radiol. 2020; 30: 6161-6169.

[188] Sociedad Española de Radiología Médica (SERAM). Guía básica de indicaciones de pruebas de imagen en la infección COVID-19. (V1. 21/3/2020); 1-9.

[189] Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020; 30: 4381-4389.

[190] Ojha V, Mani A, Pandey NN, Sharma S, Kumar S. CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients. Eur Radiol. 2020; 30: 6129-6138.

[191] Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, *et al*. Chest CT findings in coronavirus disease 2019 (COVID-19): relationship to duration of infection. Radiology. 2020; 295: 200463.

[192] Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, *et al*. Chest CT findings in patients with coronavirus disease 2019 and its relationship with clinical features. Invest Radiol. 2020; 55: 257-261.

[193] Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, *et al*. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020; 20: 425-434.

[194] Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients. AJR Am J Roentgenol. 2020; 215: 87-93.

[195] Pan Y, Guan H, Zhou S, Wang Y, Li Q, Zhu T, *et al*. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. Eur Radiol. 2020; 30: 3306-3309.

[196] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, *et al*. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID 19). Radiology. 2020; 295: 715-721.

[197] Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, *et al*. Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology. 2020; 296: E55-64.

[198] Prokop M, van Everdingen W, van Rees Vellinga T, Quarles vanUfford J, Stöger L, Beenen L, *et al*. CO-RADS - a categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology. 2020; 296: E97-104.

[199] Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, *et al*. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020; 55: 327-331.

[200] Lin L, Li TS. [Interpretation of ‘‘Guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by the national health commission (Trial Version 5)’’]. Zhonghua YiXue Za Zhi. 2020; 100: 805-7.

[201] Wang J, Xu Z, Wang J, Feng R, An Y, Ao W, *et al*. CT characteristics of patients infected with 2019 novel coronavirus: association with clinical type. Clin Radiol. 2020; 75: 408-414.

[202] Majidi H, Niksolat F. Chest CT in patients suspected of COVID-19 infection: A reliable alternative for RT-PCR. Am J Emerg Med. 2020; 38(12): 2730-2732.

[203] Long C, Xu H, Shen Q, *et al*. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. 2020; 126: 108961.

[204] Tang YW, Schmitz JE, Persing DH and Stratton CW: Laboratory diagnosis of COVID-19: Current issues and challenges. J Clin Microbiol 58: e00512-e00520, 2020.

[205] Zhang Y, Shen H, Wang X, Shi X, Li Y, *et al*. Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. Emerg Microbes Infect. 2020; 9: 833-836.

[206] Bond K, Nicholson S, Hoang T, Catton M, Howden B, Williamson D. Post-market validation of three serological assays for COVID-19. Office of Health Protection, Commonwealth Government of Australia. 2020.

[207] Tagajdid R, Konzi C, El Kochri S, Elannaz H, Abi R, Touil N, Ennibi K, Idriss Lahlou A. Evaluation of performance of nine serological assays for the detection of SARS-COV-2 antibodies. International Journal of Scientific Research. 2021; 60-62.

[208] Annweiler C, Sacco G, Salles N, Aquino JP, Gautier J, Berrut G, *et al*. National French Survey of Coronavirus Disease (COVID-19) symptoms in people aged 70 and over. Clin Infect Dis. 2021; 72(3): 490-494.

[209] Fistera D, Härtl A, Pabst D, *et al*. What about the others: differential diagnosis of COVID-19 in a German emergency department. BMC Infect Dis. 2021; 21(1): 969.

[210] Allali G, Marti C, Grosgurin O, Morelot-Panzini C, Similowski T, Adler D. Dyspnea: the vanished warning symptom of COVID-19 pneumonia. J Med Virol. 2020; 92(11): 2272-2273.

[211] Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of “happy” hypoxemia in COVID-19. Respir Res. 2020; 21(1): 198.

[212] Koo HJ, Lim S, Choe J, Choi SH, Sung H, Do KH. Radiographic and CT features of viral pneumonia. Radiographics. 2018; 38(3): 719–739.

[213] Yuan Y, Tao XF, Shi YX, Liu SY, Chen JQ. Initial HRCT findings of novel influenza A (H1N1) infection. Influenza Other Respir Viruses. 2012; 6(6): e114-e119.

[214] Wang QL, Zhang ZY, Shi YX, Jiang YB. Emerging H7N9 influenza A (novel reassortant avian-origin) pneumonia: radiologic findings. Radiology. 2013; 268(3): 882-889.

[215] Bonny V, Maillard A, Mousseaux C, Plaçais L, Richier Q. COVID-19: Pathogenesis of a multi-faceted disease. Rev Med Interne. 2020; 41(6): 375-389.

[216] Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, *et al*. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020; 395(10235): 1517-1520.

[217] Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, *et al*. Azithromycin in the treatment of COVID-19: a review. Expert Rev Anti Infect Ther. 2021; 19(2): 147-163.

[218] Taxonera C, Sagastagoitia I, Alba C, Mañas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. Aliment Pharmacol Ther. 2020; 52: 276-283.

[219] Russell CD, Millar JE and Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020; 395: 473-475.

[220] Sinha N, Balayla G. Hydroxychloroquine and COVID-19. Postgrad Med J. 2020; 96: 550-555.

[221] Gautret P, Lagier JC, Parola P, *et al*. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis. 2020; 34: 101663.

[222] Ennibi K, Kasmy Z, Reggad A, Laatiris A, Aadi Y, Nachite A, *et al*. Evaluation of the efficacy of the combination of hydroxychloroquine and azithromycin in the treatment of Covid-19 in a Moroccan Population. J Bacteriol Mycol. 2021; 8(3): 1174.

[223] Lamback EB, Oliveira MA, Haddad AF, *et al*. Hydroxychloroquine with azithromycin in patients hospitalized for mild and moderate COVID-19. Braz J Infect Dis. 2021; 25(2): 101549.

[224] Zhan WQ, Li MD, Xu M and Lu YB. Successful treatment of COVID-19 using extracorporeal membrane oxygenation, a case report. Eur Rev Med Pharmacol Sci. 2020; 24: 3385-3389.

[225] Solaimanzadeh I. Acetazolamide, nifedipine and phosphodiesterase inhibitors: Rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19). 2020; Cureus 12: e7343.

[226] Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, *et al*. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest. 2020; 130: 2757-2765.

[227] Yi C, Sun X, Ye J, Ding L, Liu M, Yang Z, Lu X, Zhang Y, Ma L, Gu W, *et al*. Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell Mol Immunol. 2020; 17: 621-630.

[228] Guang C, Phillips RD, Jiang B, Milani F: Three key proteases-angiotensin-I-converting enzyme (ACE), ACE2 and renin-within and beyond the renin-angiotensin system. Arch Cardiovasc Dis. 2012; 105: 373-385.

[229] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA. 2020; 323: 1824.

[230] Nitulescu GM, Paunescu H, Moschos SA, Petrakis D, Nitulescu G, *et al*. Comprehensive analysis of drugs to treat SARS-CoV-2 infection: Mechanistic insights into current COVID-19 therapies (Review). Int J Mol Med. 2020; 46: 467-488.

[231] Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 2020; 43: 219-222.

[232] Zhang YM, Yu L, Tang L, Zhu M, Jin Y, Wang Z, Li L. A promising anti-cytokine-storm targeted therapy for COVID-19: The artificial-liver blood-purification system. Engineering (Beijing). 2021; 7(1): 11-13.

[233] Yang XH, Sun RH, Zhao MY, Chen EZ, Liu J, *et al*. Expert recommendations on blood purification treatment protocol for patients with severe COVID-19. Chronic Dis Transl Med. 2020; 6: 106-114.

[234] Cao Y, Liu Y, Shang J, Yuan Z, Ping F, Yao S, Guo Y, Li Y. Ang-(1-7) treatment attenuates lipopolysaccharide-induced early pulmonary fibrosis. Lab Invest. 2019; 99: 1770-1783.

[235] Song JC, Wang G, Zhang W, Zhang Y, Li WQ, Zhou Z. People's Liberation Army Professional Committee of Critical Care Medicine, Chinese Society on Thrombosis and Haemostasis: Chinese expert consensus on diagnosis and treatment of coagulation dysfunction in COVID-19. Mil Med Res. 2020; 7: 19.

[236] Cohen MS. Hydroxychloroquine for the prevention of Covid-19 - Searching for Evidence. N Engl J Med. 2020; 383(6): 585-586.

[237] Ahmad S, Hafeez A, Siddqui SA, Ahmad M, Mishra S. A Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments and Prevention. EJMO. 2020; 4(2): 116–125.

[238] Manoharan L, Olliaro P, Horby PW, Watson CH. Chemoprophylaxis trial designs in epidemics: insights from a systematic review of COVID-19 study registrations. Trials. 202; 22(1): 370.

[239] Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents. 2007; 30: 297-308.

[240] Boulware DR, Pullen MF, Bangdiwala AS, *et al*. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020; 383: 517-525.

[241] Ndwandwe D, Wiysonge CS. COVID-19 vaccines. Curr Opin Immunol. 2021; 71: 111-116.

[242] Nagy A, Alhatlani B: An overview of current COVID-19 vaccine platforms. Comput Struct Biotechnol J. 2021; 19: 2508-2517.

[243] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z *et al*. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; 369: 77-81.

[244] Rodrigues AF, Soares HR, Guerreiro MR, Alves PM, Coroadinha AS. Viral vaccines and their manufacturing cell substrates: new trends and designs in modern vaccinology. Biotechnol J. 2015; 10: 1329-1344.

[245] Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis. 2020; 20: 515-516.

[246] Xing YH, Ni W, Wu Q, Li WJ, Li GJ, *et al*. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. J Microbiol Immunol Infect. 2020; 53: 473-480.

[247] Lemaire D, Barbosa T, Rihet P. Coping with genetic diversity: the contribution of pathogen and human genomics to modern vaccinology. Braz J Med Biol Res. 2012; 45: 376-385.

[248] Keech C, Albert G, Cho I, Robertson A, Reed P, *et al*. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. N Engl J Med. 2020; 383: 2320-2332.

[249] Callaway E. The race for coronavirus vaccines: a graphical guide. Nature. 2020; 580: 576-577.

[250] Mavundza EJ, Wiyeh AB, Mahasha PW, Halle-Ekane G, Wiysonge CS. A systematic review of immunogenicity, clinical efficacy and safety of human papillomavirus vaccines in people living with the human immunodeficiency virus. Hum Vaccin Immunother. 2020; 16: 426-435.

[251] Rauch S, Jasny E, Schmidt KE, Petsch B. New vaccine technologies to combat outbreak situations. Front Immunol. 2018; 9: 1963.

[252] Tomori O, Kolawole MO. Ebola virus disease: current vaccine solutions. Curr Opin Immunol. 2021; 71: 27-33.

[253] 40 11. Frederiksen LSF, Zhang Y, Foged C, Thakur A. The long road toward COVID-19 herd immunity: vaccine platform technologies and mass immunization strategies. Front Immunol. 2020; 11: 1817.

[254] Zhu L, Xu X, Ma K, Yang J, Guan H, Chen S, Chen Z, Chen G. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant. 2020; 20: 1859-1863.

[255] Qu R, Ling Y, Zhang YH, Wei LY, Chen X, *et al*. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. 2020; 92(9): 1533-1541.

[256] Pannull F, Yenull T, Sun P, Gui S, Liang B, *et al*. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology. 2020; 295: 715-721.

[257] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L and Zheng C: Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 13: 200370, 2020.

[258] Lin X, Gong Z, Xiao Z, Xiong J, Fan B, Liu J. Novel coronavirus pneumonia outbreak in 2019: Computed tomographic findings in two cases. Korean J Radiol. 2020; 21: 365-368.

[259] Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020; 55: 327-331.

[260] Qiao XM, Xu XF, Zi H, Liu GX, Li BH, Du X, Tian ZH, Liu XY, Luo LS, Wang X. Re-positive cases of nucleic acid tests in discharged patients with COVID-19: A follow-up study. Front Med (Lausanne). 2020; 7: 349.

[261] Family - Coronaviridae, Ed. King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ. Virus Taxonomy. Elsevier. 2012; Part II: 806-828

Serment d'Hippocrate

Au moment d'être admis à devenir membre de la profession médicale,
je m'engage solennellement à consacrer ma vie au service de l'humanité.

- *Je traiterai mes maîtres avec le respect et la reconnaissance qui leur sont dus.*
- *Je pratiquerai ma profession avec conscience et dignité. La santé de mes malades sera mon premier but.*
- *Je ne trahirai pas les secrets qui me seront confiés.*
- *Je maintiendrai par tous les moyens en mon pouvoir l'honneur et les nobles traditions de la profession médicale.*
- *Les médecins seront mes frères.*
- *Aucune considération de religion, de nationalité, de race, aucune considération politique et sociale ne s'interposera entre mon devoir et mon patient.*
- *Je maintiendrai le respect de la vie humaine dès la conception.*
- *Même sous la menace, je n'userai pas de mes connaissances médicales d'une façon contraire aux lois de l'humanité.*

Je m'y engage librement et sur mon honneur.

قسم أبقراط

بسم الله الرحمن الرحيم

أقسم بالله العظيم

في هذه اللحظة التي يتم فيها قبولي عضوا في المهنة الطبية أتعهد علانية:

- بأن أكرس حياتي لخدمة الإنسانية.
- وأن أحترم أساتذتي وأعترف لهم بالجميل الذي يستحقونه.
- وأن أمارس مهنتي بوازع من ضميري وشرفي جاعلا صحة مريضي هدفي الأول.
- وأن لا أفشي الأسرار المعهودة إلي.
- وأن أحافظ بكل ما لدي من وسائل على الشرف والتقاليد النبيلة لمهنة الطب.
- وأن أعتبر سائر الأطباء إخوة لي.
- وأن أقوم بواجبي نحو مرضاي بدون أي اعتبار ديني أو وطني أو عرقي أو سياسي أو اجتماعي.
- وأن أحافظ بكل حزم على احترام الحياة الإنسانية منذ نشأتها.
- وأن لا أستعمل معلوماتي الطبية بطريق يضر بحقوق الإنسان مهما لاقيت من تهديد.
- بكل هذا أتعهد عن كامل اختيار و مقسما بالله.

والله على ما أقول شهيد

المملكة المغربية
جامعة محمد الخامس بالرباط
كلية الطب والصيدلة
الرباط

سنـة : 2021 **أطروحة رقم:401**

الجوانب السريرية والمورفولوجية لمرضى كوفيد -19 المعالجون بمركز علم الفيروسات والأمراض التعفنية والاستوائية
بصدد 186 حالة

أطروحة
قدمت ونوقشت علانية يوم : / /2021

من طرف

السيدة ياسمين متمير
المزدادة في 24 يونيو 1996 بباريس
طبيبة داخلية بالمركز الاستشفائي الجامعي ابن سينا بالرباط
من المدرسة الملكية لمصلحة الصحة العسكرية بالرباط

لـنـيـل شـهـادة
دكـتـور فــي الطب

الكلمات الأساسية : كوفيد-19؛ الجوانب السريرية؛ الجوانب المورفولوجية

أعضاء لجنة التحكيم:

السيد هشام هرموش أستاذ في الطب الباطني	**رئيس**
السيد خالد النيبي أستاذ في الطب الباطني	**مشرف**
السيد أحمد ركاد أستاذ في الأمراض التعفنية والمعدية	**عضو**
السيدة منى معمر أستاذة في الطب الباطني	**عضو**
السيد يوسف أخواض أستاذ في الأمراض التعفنية والمعدية	**عضو**