Université de Bourgogne
UFR des Sciences de Santé
Circonscription Médecine

ANNEE 2021

N°

« Facteurs pronostiques de la COVID-19 chez les patients de plus de 75 ans : Etude observationnelle multicentrique »

THESE

présentée

à l'UFR des Sciences de Santé de Dijon
Circonscription Médecine

et soutenue publiquement le 7 avril 2021

pour obtenir le grade de Docteur en Médecine

par Geoffrey ODILLE

Né le 09/01/1990

A Troyes

Université de Bourgogne

UFR des Sciences de Santé

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SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

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Au Dr Sanchez, merci d'avoir accepté de faire partie de mon Jury de thèse.

A ma famille, évidement et pleinement.

A mes amis qui se reconnaitront sans aucun doute. Encore de beaux moments à vivre ensemble.

A ma femme …. et ma fille. △

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Accident vasculaire cérébral (AVC)

Activities of daily living (ADL)

Alanine amino transferase (ALAT)

Antagoniste des récepteurs de l'angiotensine 2 (ARA 2)

Aspartate aminotransferase (ASAT)

Area under receiver operating characteristics curve (AUROC)

Battements par minutes (BPM)

Bronchopneumathie chronique obstructive (BPCO)

Coronarovirus Disease 2019 (COVID-19)

Cardiac troponin I (cTnI)

Cytokine kinase (CK)

Protéine C-réactive (CRP)

Electrocardiogramme (ECG)

Fibrillation atriale (FA)

Hazard ratio (HR)

High sensitivity (HS)

Intervalle de confiance (IC)

Inhibiteur de l'enzyme de conversion (IEC)

Insuffisance rénale aigue (IRA)

Lactate deshydrogenase (LDH)

National Early Warning Score 2 (NEW score2)

NT pro Brain Natriuretic Peptide (NT-ProBNP)

Organisation mondiale de la santé (OMS)

Pneumonia severity index (PSI)

Polymerase chain reaction (PCR)

Quick Sequential Organ Failure Assessment (qSOFA)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Syndrome coronarien aigu (SCA)

Syndrome de détresse respiratoire aiguë (SDRA)

World health organization (WHO)

1 Introduction

En décembre 2019, dans le Sud de la Chine, une infection causée par un nouveau type de coronavirus appelé *Severe Acute Respiratory Syndrome* (SARS-CoV-2) émerge.[1] Deux mois plus tard celui-ci est responsable d'une pandémie mondiale motivant la mise en place de confinements afin d'endiguer sa propagation. Dans le monde, entre janvier et juillet 2020, sur 8 483 036 cas confirmés, 19,4% ont entre 65 et 84 ans et 3,4% ont plus de 85 ans.[2] Malgré le confinement, l'épidémie continue d'évoluer et est responsable à ce jour de plus de 2 millions de décès dans le monde et notamment dans la population âgée.[3] La mortalité augmente de façon majeure chez les patients de plus de 60 ans, jusqu'à l'âge de 80 ans. Il est cependant difficile d'estimer un taux de mortalité mondiale en fonction de l'âge du fait de la qualité hétérogène des recueils et des différences entre les pays.[4] Néanmoins une étude réalisée dans 5 pays (Chine, Italie, Etats Unis, Royaume-Unis et Espagne) objective que 29,6% des décès se produisent chez les patients de plus de 80 ans et 22,8% chez les patients de 70 à 79 ans.[5] L'infection à SARS-CoV-2 est devenue, tout comme la pneumonie bactérienne, une pathologie grave du sujet âgé.[6]

Ainsi, devant l'ampleur de la situation, les études de cohorte se multiplient afin de mettre en évidence des facteurs de risque qui permettraient de détecter et prévenir les formes graves. On pourrait alors plus précocement orienter le patient entre l'ambulatoire et l'hospitalier, puis au sein de l'hôpital entre les services de médecine et la réanimation.

Plusieurs facteurs de risque d'évolution défavorable sont mis en évidence telles que l'hypertension, le diabète, la bronchopneumopathie chronique obstructive (BPCO), les maladies cardiovasculaires et cérébro-vasculaires, autant de comorbidités souvent présentes et cumulées chez la personne âgée.[7, 8]

Dans la littérature, les marqueurs biologiques à l'admission pouvant prédire l'évolution intra hospitalière de la maladie ont été recherchés en population générale, mettant en évidence une élévation des D-Dimères, des biomarqueurs cardiaques, des leucocytes, des marqueurs inflammatoires et de la ferritine comme autant de marqueurs pronostiques à court terme.[9] Cependant ces résultats sont-ils extrapolables en population dite « gériatrique » où le vieillissement physiologique et l'accumulation de comorbidités peuvent modifier le niveau de base et la cinétique des différents biomarqueurs ?[10]

L'élaboration de scores pronostiques est nécessaire pour prédire l'évolutivité d'une pathologie et ainsi orienter les patients dans les différents services. Cela est particulièrement vrai en période de pandémie où les ressources hospitalières et réanimatoires sont limitées.[11] Dans la pneumopathie aigue

communautaire, plusieurs scores pronostiques ont été créés afin de permettre d'évaluer la sévérité des pneumonies aigues communautaires , le plus utilisé étant l'index de Fine (PSI). [12] Malheureusement, ce score est relativement complexe d'utilisation en pratique courante et sous-estime le risque de décès dans les pneumopathies virales.[13] D'autres scores, comme le *National Early Warning Score* (NEW score2), le *Quick Sequential Organ Failure Assessement* (qSOFA), plus récents, ont été proposés dans la *Coronarovirus Disease 2019* (COVID-19).[14] Qu'en est-il de la validité de ces scores en population âgée et hospitalisée pour une infection à SARS-CoV-2 ?

Notre étude a pour objectif de déterminer, à visée pronostique, la valeur des facteurs de gravités connus, la pertinence des marqueurs biologiques et des examens complémentaires, ainsi que la fiabilité des scores habituels mis en place pour les pneumonies bactériennes, spécifiquement dans une population âgée hospitalisée pour la COVID-19.

2 Matériel et méthodes

2.1 Type d'étude

Il s'agit d'une étude pronostique rétrospective multicentrique basée sur un recueil de données hospitalières réalisé lors de la première vague épidémique de la COVID-19.

2.2 Population

La population de l'étude était constituée de tous les patients de plus de 75 ans hospitalisés dans un service de médecine aigue gériatrique pour la COVID-19 avérée par un test PCR positif ou une probabilité clinique et scanographique forte selon les praticiens locaux, dans 4 centres hospitaliers différents (Dijon, Chalon sur Saône, Troyes, Auxerre) sur la période du 1er mars au 1er mai 2020.

2.3 Recueil des données

Les caractéristiques démographiques des patients (âge, sexe), les antécédents, les traitements habituels, le mode de vie et l'autonomie. via l'échelle *Activities of daily living* (ADL) (Annexe 1), le motif d'hospitalisation, la symptomatologie, les données cliniques et paracliniques à l'inclusion ont été recueillis, ainsi que le score de gravité de la COVID-19 selon l'Organisation mondiale de la santé (OMS) (Annexe 8). Les différentes complications intra hospitalières, la durée d'hospitalisation et le statut vital à la sortie ont également été colligés.

Le statut vital à un mois de l'admission, ainsi que les éventuelles réadmissions en service hospitalier de médecine aigue ont été recueillis par un entretien téléphonique systématique avec le patient, ou à défaut avec ses proches.

Pour plus de précision, l'ensemble exhaustif des variables recueillies dans notre étude est décrit dans l'annexe 9.

2.4 Les Scores pronostiques

Les performances des scores pronostics suivants ont été testées dans notre étude :

- Scores pronostiques utilisés dans la pneumonie aigue communautaire : PSI, CURB-65 et le A-DROP score. [15,16,17] (Annexe 2, 3, 4)
- Scores pronostiques développés pour les situations d'urgences dans un contexte de sepsis, de défaillances d'organes, ou de syndrome de détresse respiratoire aigüe (SDRA) : NEWS Scores 2 et le qSOFA. [18,19] (Annexe 5, 6)
- Score de comorbidités prédictif de mortalité : Score de Charlson. [20] (Annexe 7)
- Score spécifiquement développé pour la COVID-19 : Score OMS. [21] (Annexe 8)

2.5 Analyses statistiques

Les variables continues ont été décrites selon leurs médianes (espace interquartile) et comparées en analyse univariée par le test U de Mann-Whitney ou par le test t de Student. Les variables catégorielles ont été décrites en nombre absolu (pourcentage), et comparées par le test du chi2 (ou test de Fisher si approprié).

L'étude de la survenue de décès intra-hospitalier a été réalisée à partir de modèles à risques proportionnels de Cox. Les variables cliniquement pertinentes ou associées en univarié au décès (*P* <5%) ont été retenues dans le modèle multivarié, à partir duquel une sélection pas à pas descendante a été utilisée.

Les performances des biomarqueurs et scores pronostiques ont été comparées par statistique C (*Area under receiver operating characteristics curve*, AUROC)

Les différences ont été considérées significatives pour $P < 5\%$.

L'ensemble des statistiques a été réalisé grâce au Logiciel IBM® SPSS® Statistics Version 23.

3 Résultats

3.1 Population

Au total, 143 patients de plus de 75 ans atteints d'une infection à COVID-19 ont été inclus. Parmi les 143 patients, 48 (34%) sont décédés à 1 mois. 60 % des patients décédés suite à une infection à SARS-CoV-2 étaient des hommes contre 46 % dans le groupe des survivants *(P*=0.04*).* L'âge médian était de 87 ans parmi les décédés contre 86 ans parmi les survivants (*P*=0.12).

Concernant les différents centres hospitaliers, il y avait significativement plus de décès au CHU de Dijon (54% ; *P*=0.01) et moins de décès au CH de Troyes par rapport aux autres CH (22% ; *P*=0.001). Il n'y avait pas de différence significative pour les centres d'Auxerre et de Chalon sur Saône.

Dans le groupe décès, il y avait significativement plus de patients qui provenaient d'un autre service de l'hôpital que dans le groupe des survivants (33% vs 18% ; *P*=0.04). Il n'y avait cependant pas de différence significative entre les deux groupes concernant les patients venant du domicile ou d'un foyer logement.

Il n'y avait pas de différence significative en fonction de l'autonomie.

A propos des comorbidités, il y avait significativement plus de patients ayant une insuffisance hépatique chronique dans le groupe décès (8% vs 4% ; *P*=0.04), ainsi qu'une insuffisance rénale (27% vs 10% ; *P*=0.01). Les patients porteurs d'une insuffisance respiratoire étaient significativement moins représentés dans le groupe décès (4% vs 18% ; *P*=0.02). Néanmoins par rapport aux survivants, on retrouvait dans le groupe des décès un score de Charlson significativement plus élevé (3 [2-5] vs 2 [1-4] ; *P*=0.001).

Au niveau des vaccins, il s'avère que dans le groupe décès, les patients étaient significativement moins vaccinés contre la grippe que dans le groupe des survivants (33% vs 46% ; *P*=0.02).

Sur le plan des traitements habituels, on ne retrouvait pas de différence significative entre les deux groupes concernant la prise de traitement anticoagulant et antiagrégant. A noter que les patients sous corticoïdes au long court étaient significativement plus représentés dans le groupe décès. (12% vs 3% ; *P*=0.03).

Table 1: Caractéristiques des patients à l'admission (n (%) ou médiane [interquartile range])

	Survivants n=95	**Décédés n=48**	***P***
Age *(années)*	86 [81-89]	87 [83-91]	0.12
Homme	44 (46)	31 (65)	0.04
Indice de masse corporel (*kg/m²*)	24 [21-27]	25 [21-28]	0.79
Centre hospitalier			
Auxerre	14 (16)	11 (24)	0.28
Chalon sur Saône	8 (8)	2 (4)	0.34
Dijon	28 (32)	25 (54)	0.01
Troyes	45 (52)	10 (22)	0.001
Lieu de contamination			
Ambulatoire	67 (70)	31 (65)	0.47
EHPAD	27 (28)	15 (31)	0.72
Hôpital	17 (18)	16 (33)	0.04
Autonomie			
Marche seul	40 (42)	18 (37)	0.37
Marche avec aide	47 (49)	22 (46)	0.15
Confiné lit-fauteuil	6 (6)	3 (6)	0.23
Echelle ADL <3	16 (17)	11 (23)	0.38
Comorbidités			
Insuffisance cardiaque	19 (20)	13 (27)	0.34
Infarctus	18 (19)	8 (17)	0.78
Maladie cérébro-vasculaire	26 (27)	20 (42)	0.08
Maladie neuro-cognitive	38 (40)	26 (54)	0.11
Insuffisance respiratoire chronique	17 (18)	2 (4)	0.02
Diabète	20 (21)	10 (21)	0.96
Insuffisance hépatique chronique	2 (4)	5 (8)	0.04
Insuffisance rénale chronique	10 (10)	13 (27)	0.01
Cancer	20 (21)	14 (29)	0.28

Ulcère Gastro-duodenal	6 (6)	2 (4)	0.59
Maladie vasculaire périphérique	18 (19)	16 (33)	0.06
Charlson Comobidity Index	2 [1-4]	3[2-5]	0.001
Statut vaccinal			
Vaccinés contre la grippe	44 (46)	16 (33)	0,02
Vaccinés contre le pneumocoque conjugué	8 (8)	6 (12)	0.49
Vaccinés contre le pneumocoque non conjugué	4 (4)	3 (6)	0.59
Traitements habituels			
Anticoagulants	31 (33)	14 (30)	0.73
Aspirine	25 (26)	12 (25)	0.86
Autres antiagrégant plaquettaire	5 (5)	4 (8)	0.47
IEC	21 (22)	8 (17)	0.44
ARA 2	14 (15)	11 (23)	0,22
Bêtabloquant	28 (30)	19 (40)	0.24
Benzodiazepine	32 (34)	19 (40)	0.48
Inhibiteur de la pompe a proton	24 (25)	16 (34)	0.27
Corticoïdes	3 (3)	6 (12)	0.03

ADL: activities of daily living; ARA 2: antagoniste des récépteurs de l'angiotensine 2; IEC: Inhibiteur de enzyme de conversion

3.2 Caractéristiques cliniques

Dans le groupe décès, il y avait significativement plus de patients présentant un syndrome confusionnel que dans le groupe survivant (33% vs 14% ; *P*=0.01). Dans les deux groupes, on retrouvait essentiellement comme symptômes une fièvre (67% vs 64% ; *P*=0.77), des signes de détresse respiratoire aigüe (83 % vs 69% ; *P*=0.07), une toux (58% vs 51% ; *P*=0.44) mais sans différence significative entre les deux groupes. A noter que 6% des patients survivants présentaient une anosmie contre 0% dans le groupe décès (*P*=0.07).

Concernant les paramètres vitaux à l'admission, les patients décédés présentaient une fréquence cardiaque plus élevée que les patients survivants (85 [73-99] vs 77 [69-87] ; *P*=0.005) Il n'y avait pas de différence significative pour les autres paramètres, notamment pour la fréquence respiratoire.

Table 2: Présentation clinique à l'admission (n (%) ou médiane [interquartile range])

	Survivants n= 95	**Décédés n=48**	***P***
Présentation Clinique			
Délai premiers symptômes -hospitalisation *(jours)*	4 [2-8]	4 [1.5-8]	0.73
Fièvre (>38°C)	61 (64)	32 (67)	0.77
Détresse respiratoire aigue	66 (69)	40 (83)	0.07
Dyspnée	32 (34)	20 (42)	0.71
Toux	49 (51)	28 (58)	0.44
Expectorations	9 (9)	9 (19)	0.11
Confusion	14 (14)	16 (33)	0.01
Chute	19 (20)	12 (25)	0.72
Asthénie	41 (43)	16 (33)	0.25
Anorexie	12 (13)	1 (2)	0.04
Anosmie / agueusie	6 (6)	0 (0)	0.07
Rhinite	3 (3)	3(6)	0.39
Diarrhées / vomissements	10 (10)	1 (2)	0.22
Douleur abdominale	11 (12)	5 (10)	0.83
Frissons	8 (8)	4 (8)	0.98
Myalgies	12 (17)	4 (8)	0.44
Céphalées	3 (3)	1 (2)	0.70
Constantes			
Fréquence cardiaque *(/min*)	77 [69-87]	85 [73-99]	0.005
Pression systolique	134 [118-150]	132 [114-145]	0.37
Pression diastolique	69 [59-78]	70 [61-82]	0.43
Température *(°C*)	37.2 [36.7-37.8]	37.3[36.5-37.8]	0.91
Fréquence respiratoire *(/min*)	30 [22-32]	30 [23-32]	0.41

3.3 Données paracliniques

A propos de la biologie, il n'y avait pas de différence significative entre les deux groupes concernant les plaquettes, la CRP, la PCT, la natrémie, la kaliémie et le bilan hépatique. Dans le groupe décès on retrouvait significativement plus de patients ayant une albuminémie basse (30 [25-33] vs 32 [30-35] g/L ; *P*=0.006). Dans le groupe des décès, l'urémie (10 [7.3-15.9] vs 9 [6.6 vs 12.2] mmol/L ; *P*=0.037) et la créatininémie (108 [78-161] vs 88 [72-116] ; *P*=0.021) étaient significativement plus élevées que dans le groupe des survivants. De même, la calcémie était significativement plus élevée dans le groupe des patients décédés (2.41 [2.33-2.53] vs 2.34 [2.24-2.45] ; *P*=0.003).

Il ressortait dans le groupe décès un taux plus élevé de troponine IC (0.05 [0.04-2.20] vs 0.00 [0.00-0.05] ; *P*=0.02) et du *NT pro Brain Natriuretic Peptide* (Nt-ProBNP) (2655 [1172-9071] vs 1269 [337-3286] ; *P*=0.002). On ne retrouvait pas de différence significative entre les deux groupes concernant la Pa02 (70 [53-52-84] vs 76 [68-91] ; *P*=0.08) et les lactates (1.5 [1.10-2.05] vs 1.3[1-1.3] ; *P*=0.33).

Concernant les résultats scanographiques, dans le groupe des décès on retrouvait significativement plus souvent la présence de condensation alvéolaire (45 % vs 28 % ; *P*=0.04) ainsi que d'épanchements pleuraux (23% vs 8% ; *P*=0.04) dans le groupe décès. Il n'y avait cependant pas de différence significative entre les deux groupes en fonction du degré d'atteinte scanographique du parenchyme pulmonaire.

Les différentes anomalies recherchées de l'ECG étaient équivalentes dans les deux groupes.

Table 3: Résultats paracliniques à l'admission (n (%) ou médiane [interquartile range])

	Survivants n=95	**Décédés n=48**	***P***
Biologie			
Hémoglobine *(g/dL)*	12.5 [11.3-13.8]	12.8 [11.3-14.3]	0.53
Leucocytes *(G/L)*	6.5 [5.5-9.3]	7.4 [5.2-11.3]	0.27
Neutrophiles *(G/L)*	5.0 [3.6-7.4]	5.6 [3.5-10.6]	0.26
Lymphocytes *(G/L)*	0.77 [0.55-1,20]	0.75 [0.44-1.27]	0.51
Monocytes *(G/L)*	0.56 [0.39-0.87]	0.62 [0.38-0.84]	0.98
Plaquettes *(G/mL)*	203 [164-262]	183 [126-212]	0.09
CRP *(mg/L)*	52 [14-146]	67 [29-158]	0.23
Procalcitonine *(ng/L)*	0.13 [0.07-0.28]	0.23 [0.07-0.57]	0.36
Natrémie *(mmol/L)*	137 [133-140]	138 [135-141]	0.054
Glycémie *(mmol/L)*	6.4 [5.4-8.7]	6.4 [5.5-8.0]	0.64
Albuminémie *(g/L)*	32 [30-35]	30 [25-33]	0.006
Urée *(mmol/L)*	9.0 [6.6-12.2]	10.2 [7.3-15.9]	0.037
Créatinine *(umol/L)*	88 [72-116]	108 [78-161]	0.021
Calcium *(mmol/L)*	2.34 [2.24-2.45]	2.41 [2.33-2.53]	0.003
Phosphore *(mmol/L)*	0.96 [0.83-1.09]	0.92 [0.78-1.20]	0.97
Magnesium *(mmol/L)*	0.85 [0.79-0.96]	0.82 [0.70-0.94]	0.39
ASAT *(U/L)*	32 [20-48]	33 [23-63]	0.33
ALAT *(U/L)*	23 [16-35]	26 [20-41)	0.84
Bilirubine *(umol/L)*	10 [7-13]	10 [8-14]	0.35
LDH *(U/L)*	240 [195-367]	310 [223-395]	0.14
CK *(U/L)*	110 [55-300]	118 [66-381]	0.81
D-dimères *(mg/L)*	1344 [910-2520]	1560 [782-3555]	0.43
Troponines cTnI *(ug/L)*	0.00 [0.00-0.05]	0.05 [0.04-2.20]	0.02

NT pro Brain Natriuretic Peptide *(ng/ml)*	1269 [337-3286]	2655 [1172-9071]	0.002
PaO2 *(mmHg)*	76 [68-91]	70 [53-84]	0.08
Lactates *(mmol/L)*	1.3 [1.00-1.30]	1.5 [1.10-2.05]	0.33
Scanner thoracique			
Verre dépoli	70 (73)	37 (77)	0.51
Condensation alvéolaire	27 (28)	22 (45)	0.04
Pleurésie	8 (8)	11 (23)	0.04
Crazy paving	26 (27)	16 (33)	0.15
Etendue des lésions : <10% du parenchyme	17 (18)	7 (15)	0.86
10-25% du parenchyme	21 (22)	11(23)	0.95
25-50% du parenchyme	16 (17)	10 (21)	0.83
50-75% du parenchyme	4 (4)	4 (4)	0.59
ECG			
Fibrillation atriale	18 (19)	16 (33)	0.11
QT corrigé >440 ms	7 (7)	3 (6)	0.52
Trouble de la repolarisation	10 (10)	8 (17)	0.53

ALAT: alanine amino transferase ; ASAT : Aspartate aminotransferase; CK: cytokine kinase; CRP : protéine C Réactive ECG: électrocardiogramme; LDH: lactate deshydrogenase; cTnI: cardiac troponin I phosphorylation

3.4 Traitement spécifique

Dans le groupe des survivants, les patients ayant bénéficié d'un traitement spécifique par Lopinavir/Ritanavir étaient significativement plus représentés (21% vs 2 % ; *P*=0.002). Il n'y avait pas de différence significative pour les traitements par hydroxychloroquine et corticoïdes (*P*=0.23 ; *P*=0.12).

Table 4: Traitement spécifique durant l'hospitalisation (n (%))

	Survivants n= 95	**Décédés n= 48**	***P***
Lopinavir/ritanavir	20 (21)	1 (2)	0.002
Hydroxychloroquine	5 (5)	4 (8)	0.23
Corticoïdes	8 (8)	8 (17)	0.12
Antibiotiques	**n=73**	**n=38**	
Piperacilline/ Tazobactam	3 (3)	6 (12)	0.03
Amoxocilline / Clavulanate	22 (23)	16 (33)	0.19
Cephalosporine de 3ème génération	50 (53)	27 (56)	0.68
Fluoroquinolone	7(7)	2 (4)	0.45
Macrolide	34 (36)	18 (37)	0.84

3.5 Antibiothérapie

Dans notre étude, 38 (79%) patients du groupe décédés avaient bénéficié d'une antibiothérapie introduite à l'admission contre 73 (77%) du groupe survivant. Comme le montre la courbe de survie ci-dessous (Figure 1), il n'y avait pas de différence significative de mortalité à 1 mois entre les deux groupes. Des résultats similaires étaient retrouvés après ajustement sur le score de gravité OMS, l'indice de comorbidités de Charlson, le sexe et l'âge. (Annexe 9)

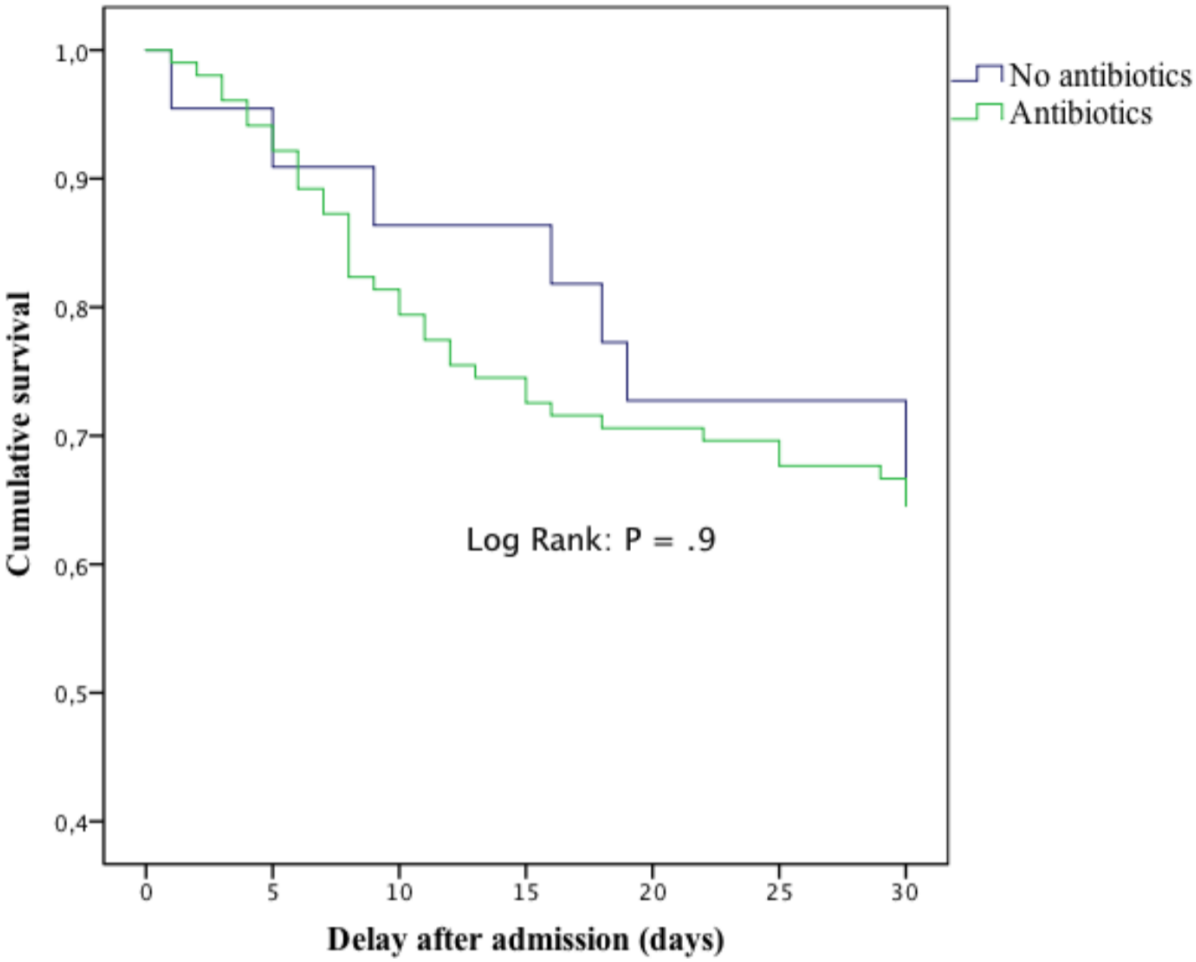

Figure 1 : Courbe de survie à 1 mois après l'admission chez des patients âgés hospitalisés pour une pneumonie à SARS-CoV-2 avec ou sans antibiotique

3.6 Complications intra hospitalières et devenir

Dans le groupe décès, il y avait significativement plus de SDRA (65 % vs 1% ; *P*=0.001) ainsi que de chocs septiques (12 % vs 0% ; *P*=0.002). Il n'y avait pas de différence significative entre les deux groupes concernant les autres complications durant l'hospitalisation.

On ne retrouvait pas de différence significative de durée d'hospitalisation entre les deux groupes, la médiane étant de 12 jours pour le groupe des survivants et 8 jours pour le groupe décès (*P*=0.14).

Parmi les patients décédés à un mois, 77% étaient décédés dans le service de gériatrie de la COVID-19. Parmi les patients survivants, 46% sont rentrés à domicile, 52% ont été transférés en convalescence et 3% ont été pris en charge en soins palliatifs.

44% des patients du groupe décès contre 3 % du groupe des survivants bénéficiaient de soins palliatifs (*P*<0.001).

De façon intéressante, sur les 142 patients de notre étude, il n'y avait aucun transfert en réanimation.

Table 5 : Complications intra-hospitalières et devenir (n (%) ou médiane [interquartile range])

	Survivants n=95	**Décédés n=48**	***P***
Complications intra-hospitalières			
Syndrome de détresse respiratoire	1 (1)	31 (65)	< 0.001
Décompensation cardiaque aigue	16 (17)	9 (19)	0.20
Maladie thrombo-embolique	3 (3)	6 (12)	0.06
SCA	3 (3)	2 (4)	0.72
FA	2 (2)	4 (8)	0.17
AVC	1 (1)	3 (6)	0.16
IRA	13 (14)	13 (27)	0.11
Choc septique	0 (0)	6 (12)	0.002
Bactériémie	3 (3)	3 (6)	0.53
Colite à C. difficile	2 (2)	0 (0)	0.46
Chute	3 (3)	5 (10)	0.16
Syndrome confusionnel	11 (11)	9 (19)	0.40
Devenir			
Durée de l'hospitalisation *(jours)*	12 [8-18]	8 [4-18]	0.14
Décès intra-hospitalier	0	37 (77)	< 0.001
Retour à domicile	44 (46)	2 (4)	< 0.001
Centre de convalescence	49 (52)	5 (10)	< 0.001
Prise en charge palliative	3 (3)	21 (44)	< 0.001
Unité de soins intensifs	0	0	1

AVC: accident vasculaire cérébral; FA: fibrillation auriculaire; IRA: Insuffisance réanale aigue; SCA: syndrome coronarien aigu

3.7 Courbes de survie en fonction de la sévérité de la pathologie à l'admission selon la classification OMS

La courbe de survie mettait en évidence l'excellente valeur prédictive de décès à un mois dans les formes de pneumonies reconnues sévères et très sévères selon la stratification OMS à l'admission. Dans les cas très sévères (OMS 4) on observait environ 80 % des décès à 15 jours d'hospitalisation, et 40 % pour les formes sévères (OMS 3) .

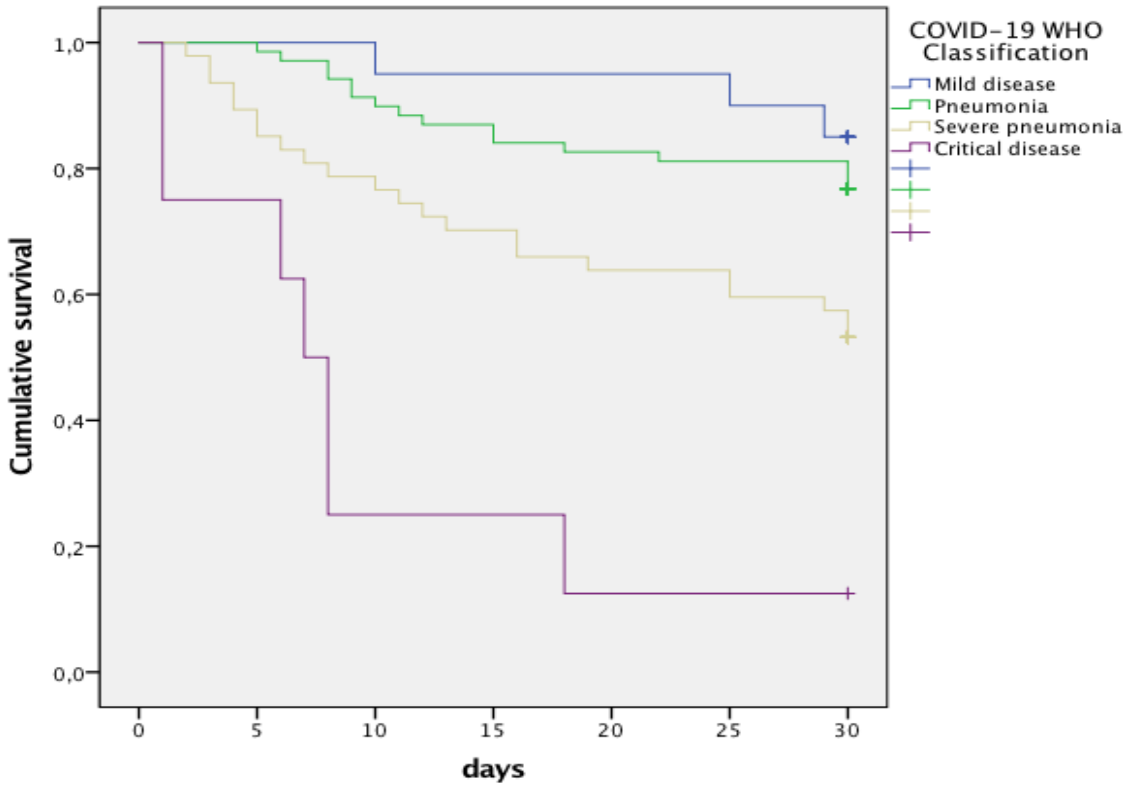

Figure 2 : Courbe de survie à 1 mois en fonction du score OMS

3.8 Analyse multivariée des facteurs associés à la mortalité à 1 mois

Après ajustement sur les comorbidités, l'analyse multivariée montre que l'âge était un facteur de risque indépendant de décès (Hazard Ratio (Intervalle de confiance à 95%) : (HR(IC95%)) 1.07 (1.00-4.88) ; *P*=0.045), tout comme le sexe masculin (HR (IC95%) 2.21 (1.00-4.88) ; *P*=0.049), la valeur du score OMS (HR (IC95%) 2.23 (1.31-3.80) ; *P*=0.003), le score de Charlson (HR (IC95%) 1.16 (1.02-1.30) ; *P*=0.021) et la fréquence cardiaque (HR (IC95%)) 1.02 (1.00-1.04) ; *P*=0.040).

Table 7: Analyse multivariée des facteurs associés à la mortalité à 1 mois

Variables	**Hazard Ratio (95% intervalle de confiance)**	***P***
Score OMS (*par point*)	2.23 (1.31-3.80)	0.003
Homme	2.21 (1.00-4.88)	0.049
Age (*années*)	1.07 (1.00-1.14)	0.045
Score de Charlson (*par point*)	1.16 (1.02-1.30)	0.021
Fréquence cardiaque (*bpm)*	1.02 (1.00-1.04)	0.040

bpm: battement par minute

3.9 Outils pronostiques

Parmi les 6 scores testés dans notre étude , le score PSI était celui dont la prédiction de la mortalité semblait la plus fiable (tableau 6) (AUROC (IC95%)) 0.74 [0.60-0.88]), suivi par le score OMS (AUROC (IC95%)) 0.70 [0.60-0.79]), le score de Charlson (AUROC (IC95%)) 0.66 [0.58-0.76]), le NEWS 2 (AUROC (IC95%)) 0.66 [0.58-0.76]), puis du qSOFA (AUROC (IC95%)) 0.61 [0.50-0.72]) et enfin le CURB 65 (AUROC (IC95%)) 0.51 [0.40-0.62]) .

La sensibilité du score de Charlson était bonne à 92 % pour un *cut off* supérieur ou égal à 2. La sensibilité du score de PSI était modérée à 87 % pour un *cut off* supérieur ou égal à 128. Un score OMS ≥ 3, un NEWS 2 ≥ 9 , un qSOFA ≥ 2, ou un CURB 65 ≥ 3, avaient une sensibilité faible pour identifier les patients à risque de décès. La spécificité pour identifier les patients survivants était modérée pour un score NEWS 2 coté ≥9 (87%) et un qSOFA≥2 (83%). Le WHO score ≥3 (60%), le PSI ≥128 (57%), le CURB 65 ≥3 (46%), et le CCI ≥2 (36%) possèdent une spécificité basse.

Concernant les biomarqueurs, le NT-proBNP semblait le marqueur prédictif le plus fiable (AUROC 95% IC 0.71 [0.60-0.82], suivi de la troponine (AUROC (IC95%)) 0.70 [0.55-0.85]) et de l'albuminémie (AUROC (IC95%)) 0.69 [0.57-0.81]).

La sensitivité du NT-proBNP était à 94% pour un *cut off* ≥ 674 ng/ml contre une sensitivité à 64% pour un *cut off* ≥ 2122 ng/ml. La sensitivé de la troponine ≥ 0.05 ug/L était à 62% et celle de l'albumine ≥ 2.75 dg/L à 39% .

Table 6: Prédiction à 30 jours de la mortalité des Scores pronostiques et des biomarqueurs à l'admission

	AUROC [IC95%]	Cut-off	Sensibilité	Spécificité
Scores pronostiques				
Pneumonia Severity Index	0.74 [0.60-0.88]	128	87%	57%
WHO Score	0.70 [0.60-0.79]	3	60%	73%
CCI	0.66 [0.58-0.76]	2	92%	36%
NEWS2	0.66 [0.55-0.77]	9	45%	87%
A DROP	0,65[0.55-0.75]			
qSOFA	0.61 [0.50-0.72]	2	37%	83%
CURB65	0.51 [0.40-0.62]	3	60%	46%
Biomarqueurs				
NT Pro-BNP (*pg/mL*)	0.71 [0.60-0.82]	674	94%	46%
		2122	64%	65%
		5503	39%	89%
Troponine Ic (*µg/L*)	0.70 [0.55-0.85]	0.05	62%	75%
Albumine (*g/dL*)	0.69 [0.57-0.81]	2.75	39%	6%
		3.35	16%	59%

AUROC: *Area under the receiver operating characteristic curve*; CCI: *Charlson comorbidity index*; IC: Intervalle de confiance; NtPro-BNP: *N terminal Pro brain natriuretic peptide*; NEWS2: *National early warning score 2*

4 Discussion

Cette étude rétrospective réalisée chez des patients très âgés hospitalisés pour une infection à SARS-CoV-2 met en évidence plusieurs facteurs de mortalité à 1 mois : Les patients décédés présentaient plus fréquemment un syndrome confusionnel et une tachycardie à l'admission, mais la fréquence respiratoire ne différait pas significativement entre les deux groupes. La présence d'une condensation alvéolaire ou d'un épanchement pleural au scanner était significativement associée au décès. Concernant les biomarqueurs, le Nt-proBNP et la troponine présentaient la meilleure valeur pronostique parmi les examens biologiques usuels. Enfin parmi les scores pronostiques, les Score PSI et OMS présentaient les meilleures performances dans notre population.

Concernant les conditions prédisposantes, l'analyse multivariée mettait en évidence l'âge, le sexe masculin ainsi que les comorbidités appréciées par le score de Charlson comme facteurs de risque de mortalité intra hospitalière.

De façon alarmante, il n'y avait aucun transfert en service de réanimation malgré la mortalité majeure, évaluée à un tiers des patients hospitalisés à un mois. Une prise en charge palliative était proposée pour près de la moitié des patients décédés.

Dans notre étude, la surmortalité masculine était très significative. Cette information est largement retrouvée dans la littérature,[22,23,24] d'une part du fait sans doute d'une plus grande comorbidité, notamment cardiovasculaire à âge égal chez l'homme, d'autre part plusieurs études ont suggéré que le SARS-CoV-2 infecte préférentiellement les hommes.[25, 26] Plusieurs hypothèses ont été proposées pour expliquer ce sur-risque masculin, comme le rôle du chromosome X dans l'immunité innée ou la surexpression des récepteurs de conversion de l'angiotensine (ARC) dans les poumons des patients de sexe masculin, récepteurs privilégiés de fixation du virus.[27, 28]

L'âge est effectivement un facteur de risque important dans les maladies respiratoires, résultant de l'immunosénescence et en particulier de l'altération de l'immunité humorale.[29,30] A noter dans notre étude l'absence de différence significative entre les deux groupes concernant le taux sérique de lymphocytes, contrairement à une étude chez 244 patients à Wuhan.[29] En effet, comme le suggère une autre étude chez le sujet jeune, la lymphopénie est fréquemment associée à un mauvais pronostic.[31] Cette différence avec nos résultats est peut-être en lien avec l'âge bien plus avancé de notre population ou peut être avec un manque de puissance de notre étude. Cependant une étude Suisse réalisée sur des patients présentant une moyenne d'âge de 86 ans retrouvait elle aussi la présence d'une lymphopénie plus importante dans le groupe décès.[32]

L'appréciation de l'état de santé des patients âgés se fait de plus en plus sur leur réserve fonctionnelle et non plus simplement sur leurs maladies.[33] De par le vieillissement, les capacités fonctionnelles diminuent et les comorbidités émergent, pouvant expliquer une plus grande vulnérabilité aux évènements extérieurs tels que la COVID-19.[34] Il nous parait donc important de ne pas attribuer de manière simpliste l'augmentation des complications liées à la COVID-19 à l'âge chronologique, mais bien de cibler les comorbidités prédisposantes, même intriquées, afin de mieux repérer, au sein de la population très âgée, les sujets les plus à risques.[Erreur ! Signet non défini.] Dans notre é tude, le risque global lié aux comorbidités était apprécié par le score de Charlson.[20] De façon attendue, le score était significativement associé à un surrisque de mortalité à un mois. Des résultats similaires dans une cohorte nord-américaine de 1305 patients infectés par le SARS-CoV-2 avec une moyenne d'âge de 61 ans, mettait en évidence une mortalité augmentée pour un score de Charlson supérieur à 3. [35] Dans la littérature, deux des principales comorbidités considérées comme des facteurs de risque de mauvais pronostic lors d'une infection à SARS-CoV-2 sont les maladies cérébro-vasculaires et les maladies cardio-vasculaires.[36] Dans notre étude, malgré une forte tendance, il n'y avait pas de différence significative entre les deux groupes concernant ces deux atteintes. De plus, le diabète et les insuffisances respiratoires chroniques obstructives, souvent associés à des formes plus sévères dans diverses études en population gériatrique, [7,36,37,38] n'étaient pas associées à la mortalité dans notre étude. Ces différences avec la littérature étaient possiblement dues à un manque de puissance ou plus vraisemblablement à un biais d'inclusion: Les patients présentant ce type de comorbidités sont plus facilement hospitalisés même en absence de forme grave de COVID-19.

Concernant la symptomatologie clinique, comme dans la population générale, les symptômes les plus fréquemment rencontrés dans la COVID-19 chez les personnes âgées étaient la dyspnée, la toux, la fièvre et l'asthénie sans différence significative entre nos deux groupes.[39] D'autres études portant sur des populations âgées retrouvent les mêmes résultats.[40,41] Dans notre étude, on retrouve une surreprésentation des syndromes confusionnels chez les patients décédés (toutefois non confirmée après ajustement). Ces données semblent confirmées dans la littérature.[42] Le syndrome confusionnel fait partie des signes cliniques atypiques et fréquemment rencontrés en gériatrie, pouvant rendre les diagnostics plus difficiles. En effet dans une étude multicentrique française, sur 353 patients (âge moyen : 87 ans) hospitalisés pour la COVID-19, 94 patients (26.7 %) présentaient un syndrome confusionnel.[43]Ces tableaux aspécifiques ont probablement amené à un retard de diagnostic et de prise en charge pouvant probablement expliquer l'impact pronostique.[44] Dans notre étude ainsi que dans la littérature, il n'y avait cependant pas de différence significative entre les deux groupes concernant le délai de prise charge entre patients décédés et survivants aussi bien dans la population générale que chez les personnes âgées.[45]

Dans notre étude comme dans une autre série gériatrique, [32] une fréquence cardiaque élevée à l'admission était associée à un sur-risque de décès. Il est difficile cependant d'utiliser ce résultat seul en pratique courante, la valeur seuil de 85 bpm n'étant en soi pas pathologique. Mais la fréquence cardiaque pourrait s'intégrer à de futurs scores pronostiques, comme c'est déjà le cas pour le score PSI et le NEWS Score 2. [15, 18]

Dans notre travail, on observe que les patients vaccinés contre la grippe étaient significativement moins représentés dans le groupe décès. Durant la pandémie, il a été décrit plusieurs cas de co-infections avec la grippe.[46] A ce jour il n'y a aucune donnée suggérant des manifestations cliniques différentes entre une infection à SARS-CoV-2 avec ou sans vaccination anti-grippale, ni de diminution de la mortalité liée aux campagnes de vaccination anti grippale.[47] On peut alors penser que la sur représentation des vaccinés contre la grippe dans le groupe survivants était peut être liée non pas à une protection contre la COVID-19 conférée par le vaccin mais plutôt à une diminution des conséquences d'une co-infection grippale. Cependant notre étude a débuté après l'épidémie de grippe, quasi inexistante cette année, ce qui réfute notre hypothèse. La surreprésentation des vaccinés dans le groupe des survivants est vraisemblablement liée à un facteur confondant, et possiblement le reflet d'un meilleur accès aux soins. Concernant le vaccin anti pneumococcique, il n'y avait pas de différence entre les deux groupes. On peut souligner la faible proportion de patients vaccinés contre le pneumocoque (et ce malgré les recommandations actuelles), malheureusement en cohérence avec les chiffres de la couverture vaccinale française actuelle qui représente environ 3 % de la population pour laquelle le vaccin est indiqué. [48, 49]

Un travail multicentrique réalisé dans 9 hôpitaux dans la Province de Hubai en Chine (âge médian 57 ans) a mis en évidence l'élévation des marqueurs cardiaques comme étant un facteur de mauvais pronostic.[50] Nous confirmons bien une augmentation significative du Nt-proBNP et de la troponine dans le groupe décès. Ces deux biomarqueurs présentaient les meilleures performances pronostiques dans notre étude, devant l'albumine. L'hypoalbuminémie est un marqueur très utilisé dans plusieurs spécialités et notamment gériatrique comme un critère de fragilité.[51] Il était le témoin d'une dénutrition mais peut être aussi le reflet d'un syndrome inflammatoire profond.[52] Dans notre étude, on retrouvait une albuminémie significativement plus basse dans le groupe décès que dans le groupe survivant. Ce n'était cependant pas, d'après nos résultats, le meilleur marqueur pronostic biologique à la phase aigüe de la COVID-19.

Le scanner thoracique joue un rôle précieux dans le diagnostic mais reflète également l'importance de l'atteinte pulmonaire. [53] Il n'a pas été retrouvé dans la littérature de corrélation entre mortalité et étendue des lésions pulmonaires, ce que nous confirmons dans notre étude,

contrairement à l'étude dynamique du scanner thoracique (réalisation de minimum deux imageries thoraciques durant l'hospitalisation).[53,54] De façon intéressante, nos données retrouvent une surreprésentation de condensations alvéolaires ou d'épanchements pleuraux dans le groupe décès, résultats non décrits dans la littérature à notre connaissance. Ces images témoignent soit de surinfection bactérienne, soit plus probablement d'un processus viral déjà évolué, ces atteintes correspondant au stade tardif des pneumonies à SARS-CoV-2.[55]

Afin de prédire l'évolution clinique de la maladie de façon fiable dans cette population à risque, de nombreux scores pronostics déjà utilisés pour les infections respiratoires sont disponibles. Ces outils permettent d'anticiper une évolution défavorable, et ainsi réaliser des transferts précoces dans des unités dédiées. On soulignait plus haut à ce sujet que sur les 144 patients hospitalisés dans nos services gériatriques, il n'y avait eu aucun transfert en service de réanimation. Cependant le nombre de lits de réanimation varient considérablement d'un pays à l'autre en Europe.[56] Dans une étude italienne réalisée en Lombardie, sur 1591 patients hospitalisés en service de réanimation, l'âge médian était de 63 ans et seulement 1% des patients avaient entre 81 ans et 90 ans.[57] Dans une étude Française réalisée par le CHU de Toulouse, l'âge médian des patients hospitalisés en réanimation pour la COVID-19 était aussi de 63 ans. Ce résultat peut faire redouter une certaine sélection des patients dans nos hôpitaux durant la pandémie, en lien probablement avec l'âge.[58,59] Pour éviter une sélection -parfois observée- basée uniquement sur l'âge (qui correspondrait finalement à une situation inacceptable d'âgisme), un des rôles du gériatre en cette période de crise liée à la COVID-19 est de proposer des outils alternatifs de tri d'usage aisé, à destination notamment des urgentistes et réanimateurs.

Plusieurs travaux ont comparé l'utilisation de différents scores pronostiques dans le cadre d'une infection à SARS -CoV-2. Une étude réalisée sur 654 patients à Wuhan réalisée dans la population générale objective que le score A DROP (AUROC (IC95%) 0,87 [0,84-0.90]) semble le plus à même de prédire l'évolutivité de l'infection, suivi du CURB 65 (AUR0C (IC95%) 0,85[0.81-0.089]) et du PSI (AUROC (IC95%) 0.85 [0.81-0.88]).[60] Aucune autre étude à notre connaissance n'a évalué l'utilité du score A DROP spécifiquement chez des patients très âgés. Dans notre étude ce score semble peu performant, mais toutefois meilleur que le CURB 65.

Le score PSI présente les meilleures performances dans notre étude, cependant il est difficile à utiliser en pratique, de par son nombre d'items élevés. Le score OMS, plus facile d'utilisation, présentait des performances similaires. Il est vrai que ce score pronostique composé de 4 items seulement est très simple et rapide à utiliser en pratique clinique et pourrait être mis en place dans certains établissements comme en maison de retraite afin d'être une aide à la prise de décision de transfert lors d'une infection à SARS-CoV-2.[61]

Les limites de notre étude sont d'abord son format rétrospectif, avec l'existence de biais de recueil d'information et de données manquantes dans les dossiers, notamment concernant la vaccination et l'autonomie.

Le nombre de patients inclus, malgré le caractère multicentrique, reste limité, n'offrant pas une puissance suffisante pour une analyse fine des facteurs pronostiques secondaires.

Le suivi à un mois seulement et les données de mortalité en population gériatrique, ne permet pas d'appréhender toutes les conséquences d'un épisode aigu et de rendre compte de l'impact sur la qualité de vie. On peut penser aux infections à *Clostridioides difficile* secondaires aux traitements antibiotiques, ou encore les pertes d'indépendance à plus long terme. Le recueil des complications à un mois pour les patients sortis préalablement de l'hôpital était limité à un entretien téléphonique, et ainsi vraisemblablement sous-estimé. Toutefois la majorité des patients n'avait pas quitté le cadre hospitalier à un mois de leur admission.

Avec un âge médian des patients à 86 ans, notre étude est une des rares à notre connaissance s'intéressant à une population si âgée, pourtant extrêmement touchée durant l'épidémie. Le multicentrisme au sein de deux régions distinctes, touchées différemment par la COVID-19, et aux pratiques hétérogènes est un atout pour la validité externe de notre étude. Un autre point fort dans notre travail est la grande variété de critères étudiés, non retrouvés dans la littérature, comme l'autonomie des patients, l'existence d'une vaccination anti-grippale et anti-pneumococcique préexistante, ou encore les traitements habituels. Enfin l'étude de la performance des différents scores pronostiques existants en population très âgée pourrait découler sur une application concrète de nos résultats en pratique clinique voire l'élaboration d'un nouvel outil spécifique à la personne très âgée.

5 Conclusion

Cette étude observationnelle, multicentrique, réalisée auprès d'une population très âgée hospitalisée en service de médecine aiguë pour une infection à SARS-CoV-2, montre que l'âge, le sexe masculin et un score de Charlson >2 sont des facteurs de risque préexistants indépendants de mortalité à un mois.

Concernant la présentation initiale, l'augmentation de la fréquence cardiaque plus que la fréquence respiratoire, l'hypoalbuminémie et l'élévation des biomarqueurs cardiaques, ainsi que la présence de condensation alvéolaire ou d'épanchement pleural au scanner (mais pas le degré d'atteinte parenchymateuse) à l'admission sont des facteurs de risque de décès.

Concernant les scores pronostiques, le score PSI et le WHO score sont dans notre étude les deux outils les plus adaptés pour prédire la mortalité à 30 jours dans cette population. Le nombre très élevé d'items rend l'application clinique du PSI difficile, et fait préférer en pratique le WHO score, d'utilisation aisée.

Cette étude permet ainsi de mieux cibler les personnes très âgées à risque d'évolution défavorable après infection à SARS-CoV-2 dont un tiers conduiront au décès. La création d'un score spécifique aux patients âgés permettrait à l'avenir de stratifier le risque à court terme et d'adapter précocement la prise en charge.

ANNEXES

Annexe 1 : score ADL

Echelle d'autonomie (ADL)

ECHELLE A.D.L		Nom ..... Prénom ..... Date ..... Score .....
Hygiène Corporelle	Autonome Aide partielle Dépendant	1 ½ 0
Habillage	Autonomie pour le choix des vêtements et l'habillage Autonomie pour le choix des vêtements et l'habillage mais besoin d'aide pour se chausser. Dépendant	1 ½ 0
Aller aux toilettes	Autonomie pour aller aux toilettes, se déshabiller et se rhabiller ensuite. Doit être accompagné ou a besoin d'aide pour se déshabiller ou se rhabiller. Ne peut aller aux toilettes seul	1 ½ 0
Locomotion	Autonomie A besoin d'aide (canne, déambulateur, accompagnant) Grabataire	1 ½ 0
Continence	Continent Incontinence occasionnelle Incontinent	1 ½ 0
Repas	Se sert et mange seul Aide pour se servir, couper le viande ou peler un fruit Dépendant	1 ½ 0

Total = /6

Annexe 2 : Score PSI

Variables	**Points**	**Résultat**
Homme		
Femme	Age -10	
Maison de retraite	+ 10	
Cancer évolutif*	+ 30	
Hépatopathie chronique	+ 20	
Insuffisance cardiaque congestive	+ 10	
Maladie cérébro-vasculaire	+ 10	
Insuffisance Rénale	+ 10	
Statut mental altéré**	+ 20	
Fréquence respiratoire> 30/mn	+ 20	
TA systolique < 90 mm Hg	+ 15	
Température < 35°C ou > 39°9	+ 10	
Pulsations > 124/ min	+ 10	
Ph Artériel < 7,35	+ 30	
Urée plasmatique > 10 mMol/L	+ 20	
Natrémie < 131 mMol/L	+ 20	
Glycémie > 13 mmol/L	+ 10	
Hématocrite < 31%	+ 10	
PaO2 < 60 mm Hg***	+ 10	
Epanchement pleural	+ 10	
TOTAL		

Annexe 3 : CURB 65

CURB-65	Clinical Feature	Points
C	Confusion	1
U	Urea > 7 mmol/L	1
R	RR ≥ 30	1
B	SBP ≤ 90 mm Hg OR DBP ≤ 60 mm Hg	1
65	Age > 65	1

CURB-65 Score	Risk group	30-day mortality	Management
0 -1	1	1.5%	Low risk, consider home treatment
2	2	9.2%	Probably admission vs close outpatient management
3-5	3	22%	Admission, manage as severe

Annexe 4 : A DROP score

A-DROP	Clinical feature	Points
Age	men≥70 years, woman≥75 years	1
Dehydratation	Urea≥21 mg/dL	1
Respiratory failure	Arterial oxygen saturation ≤90%	1
Orientation disturbance	Confusion	1
Blood Pressure	Systolic blood pressure ≤90 mmHg	1

Annexe 5 : NEWS 2 score

Physiological paramete r	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Annexe 6 : qSOFA score

Assessment	qSOFA score
Low blood pressure (SBP ≤100 mmHg)	1
High respiratory rate (≥22 breaths/min)	1
Altered mentation (GCS ≤14)	1

Annexe 7 : Score de Charlson

Nombre de points attribués	Conditions
1 point	Infarctus myocardique
	Insuffisance cardiaque
	Insuffisance vasculaire périphérique
	Maladie cérébro-vasculaire
	Démence
	Maladie pulmonaire chronique
	Maladie du tissu conjonctif
	Maladie ulcéreuse
	Hépatopathies
	Diabète
2 points	Hémiplégie
	Maladie rénale modérée à sévère
	Diabète avec lésions organiques
	Tumeurs de toutes origines
3 points	Hépatopathie modérée à sévère
6 points	Tumeurs solides métastatiques
	SIDA

Annexe 8 : *Score OMS*

	Score OMS
S1	Pas de pneumonie
S2	Pneumonie avec saturation supérieur à 90% en air ambiant
S3	Pneumonie sévère avec fréquence respiratoire supérieur à 30 par minute et/ou saturation inférieur à 90% en air ambiant
S4	Etat critique avec syndrome de détresse respiratoire aigüe

Annexe 9 : Questionnaire de récolte des données de l'étude

Etude COVID-19

Nom : ***n° de téléphone :***

Prénom : ***Médecin traitant :***

Sexe : Poids (si disponible) :

Age : Taille (si disponible) :

Antécédents :

INDEX DE COMORBIDITE DE CHARLSON

Infarctus du myocarde	oui	non
Insuffisance cardiaque congestive	oui	non
Maladies vasculaires et périphériques	oui	non
Maladies cérébro-vasculaires (sauf hémiplégie)	oui	non
Trouble neurocognitifs	oui	non
Maladies pulmonaires chroniques	oui	non
Maladies du tissu conjonctif	oui	non
Ulcères gastro duodénaux	oui	non
Diabète sans complication	oui	non
Maladies hépatiques légères	oui	non
Hémiplégie	oui	non
Maladies rénales modérées ou sévères	oui	non
Diabète avec atteinte d'organe cible	oui	non
Cancer	oui	non
Leucémie	oui	non
Lymphome	oui	non

Myélome Multiple	oui	non
Maladie hépatique modérée ou sévère	oui	non
Tumeur métastasée	oui	non
SIDA	oui	non

Allergies : ☐ Oui ☐ Non

Vaccins : **Grippe** Oui Non **Pneumocoque** Oui Non

Traitement habituel :

- Anticoagulant (AVK, AOD, autres) : Oui Non
- Antiagrégant plaquettaire type Aspirine Oui Non
- Autres antiagrégant plaquettaire Oui Non
- IEC Oui Non
- ARA 2 Oui Non
- Spironolactone Oui Non
- Béta bloquant Oui Non
- Benzodiazépines Oui Non
- IPP Oui Non
- Corticoïde Oui Non

Lieu de vie : ☐Domicile ☐EHPAD ☐Foyer logement

ADL avant hospitalisation : Oui Non

Si Oui Score :

⇨ A l'admission :

Date des premiers symptômes :

Fièvre : Oui Non

Frissons : Oui Non

Céphalées : Oui Non

Myalgies : Oui Non

Dyspnée : Oui Non

Toux : Oui Non

Crachats : Oui Non

Rhinite : Oui Non

Douleur thoracique : Oui Non

Anosmie : Oui Non

Agueusie : Oui Non

Diarrhées : Oui Non

Vomissements : Oui Non

Douleurs abdominales : Oui Non

Confusion : Oui Non

Autres : ……

Constante:

- Tension artérielle :
- Pouls :
- Température :
- Fréquence respiratoire :
- Saturation :
- Oxygène :

Biologie :

- Hémoglobine : …….. g/dl
- Leucocytes :…… G/L
- Neutrophiles :……. G/L
- Lymphocytes :…… G/L
- Plaquettes :……. G/L
- Sodium :…….. mmol/L
- Potassium :…… mmol/L
- Phosphore :…….. mmol/L
- Créatinine :…….. umol/L
- Albumine :…… g/L
- Calcium corrigé :…….. mmol/L
- ASAT :…….. U/L
- ALAT :…….. U/L
- PAL :…….. U/L
- GGT :…….. U/L
- Bilirubine totale……. umol/L
- Urée ….. mmol/L
- Glycémie……. mmol/L

- Ddimères : …….. mg/L
- CRP : …… mg/L
- PCT : …….. ng/L
- TP : ……... %
- LDH :…….. U/L
- CK totale :…….. U/L
- NT-ProBNP:…….. ng/ml
- Troponine:…….. ng/ml
- Ph : ……
- PCO2 : ……. ……. mmHg
- PO2 : …… mmHg
- HCO3: ……. mmol/L
- Lactates : …… mmol/L

ECG :

- Rythme : ☐Sinusal régulier ☐Arythmie auriculaire
- Trouble de la repolarisation : Oui Non
- Trouble de la conduction : Oui Non

Autres :

TDM thoracique :

- Verre dépoli : Oui Non
- Condensation alvéolaire : Oui Non
- Épanchement pleural : Oui Non
- Adénopathie médiastinales Oui Non
- Autres ……..

PCR COVID-19 : Positive Négative

Classification OMS COVID-19 :

- S1 : Pas de pneumonie
- S2 : Pneumonie non hypoxémiente, non dyspnéisante
- S3 : Pneumonie sévère (sepsis OU O2 OU sat inf à 90% OU FR>30)
- S4 : Forme critique/ DRA / défaillance multi viscérale

⇨ Evolution intra hospitalière :

- Traitement spécifique lors de l'épisode : Oui Non

Si oui :

☐Lopinavir/ritanavir ☐Chloroquine ☐Remdisivir

☐Azythromycine ☐Augmentin ☐C3G

☐Fluoroquinolone ☐Anti inflammatoires ☐Autres :……

Si oui durée du traitement: …… jours

- Y a-t-il eu des complications **:** Oui Non

Si oui la ou lesquelles :

Syndrome coronarien aigu	oui	non
ACFA nouvelle	oui	non
Accident vasculaire cérébral	oui	non
Maladie veineuse thromboembolique	oui	non
Infection de cathéter	oui	non
SDRA	oui	non
Choc	oui	non
Chutes	oui	non
Escarres	oui	non
Insuffisance rénale aigue (augmentation de 30% de la créatinine)	oui	non
Iatrogénie	oui	non
Bactériémie	oui	non
Syndrome confusionnel	oui	non

- Durée de l'hospitalisation : …… jours

- Décès : Oui Non

Si oui cause :

- **Transfert :** Réanimation Oui Non
  SSR Oui Non
  Retour à domicile Oui Non

⇨ <u>Suivi à 1 Mois (téléphone) :</u>

- Décès : Oui Non NSP

Si oui, cause :

- Hospitalisation depuis l'épisode : Oui Non NSP
- Institutionnalisation : Oui Non NSP
- ADL : /6

Annexe 10 : Odille G, Girard N, Sanchez S, Lelarge S, Mignot A, Putot S, et al. ***Should We Prescribe Antibiotics in Older Patients Presenting COVID-19 Pneumonia?*** *Journal of the American Medical Directors Association. févr 2021;22(2):258-259.e1.*

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Research Letter

Should We Prescribe Antibiotics in Older Patients Presenting COVID-19 Pneumonia?

To the Editor:

The COVID-19 pandemic is responsible for a particularly high level of morbidity in the older population.[1] Most deaths are the result of severe viral pneumonia, for which therapeutic management is still a matter of debate. Corticosteroids are to date the only therapeutic class that has proven benefit in terms of mortality in hypoxemic SARS-CoV-2 pneumonia,[2] whereas the benefit of tocilizumab remains unclear.[3] However, such therapeutics are associated with increased risk of bacterial infection, especially among older individuals. Moreover, the distinction between bacterial and viral pneumonia is particularly difficult, and coinfections have been highlighted, although in limited proportions.[4–6] There is currently no distinctive tool to conclusively distinguish SARS-CoV-2 pneumonia from viral-bacterial coinfections, and atypical symptoms are particularly frequent in older patients.[7] Recent guidelines suggest a restrictive use of antibacterial drugs in patients with COVID-19.[6,8] However, the level of evidence for such recommendations is very low, and antibiotics are widely prescribed in practice,[4,5] especially in older patients.[9]

To our knowledge, whether systemic antibiotic therapy should be prescribed in acute pneumonia patients testing positive for COVID-19 has not been evaluated yet in a geriatric setting. In a multicenter retrospective cohort study of older patients with a SARS-CoV-2 pneumonia, we sought to assess whether the use of antibiotics was associated with lower mortality.

We included 124 consecutive patients aged ≥75 years hospitalized from March 1 to May 1, 2020, in 4 hospitals of one of the French regions most affected by the first wave of COVID-19. Patients had radiology-proven pneumonia and tested positive for SARS-CoV-2 (Real-Time Polymerase Chain Reaction Novodiag; Movidiag, Espoo, Finland). We compared mortality 1 month after admission between patients with and without antibiotic treatment (Supplementary Material).

Pneumonia was defined according to the American guidelines, in the acute presence of (1) 2 or more of the following signs: new cough, sputum production, dyspnea, pleuritic pain, abnormal temperature (<35.6°C or >37.8°C), or altered breathing sounds on auscultation and (2) a new infiltrate on chest imaging.[10]

Of the 124 patients with pneumonia, 102 (82%) received antibiotics and 22 received none. The 2 groups were similar in terms of sex (male 52% vs 48%, $P = .9$), age [median age (interquartile range): 85 (81-89) vs 86 (83-90), $P = .4$] and comorbidities [median Charlson Comorbidity Index: 2 (1-4) vs 3 (2-4), $P = .2$). However, patients with antibiotics had more severe presentation (severe or critical pneumonia according to WHO criteria[10]: 49% vs 23%, $P = .02$). Alveolar condensation was identified on the CT scan in 38% and 27%, respectively ($P = .3$). The antibiotic regimens included third-generation cephalosporins (3GC) (75 patients), macrolides (50 patients), penicillin + beta-lactamase inhibitor (40 patients), and fluoroquinolones (9 patients). Antibiotic associations were frequent, especially 3GC with macrolides (45 patients).

As shown in Figure 1, mortality rates did not significantly differ between the 2 groups at 1 month (36% of death in both groups; $P > .99$). After adjustment on WHO severity classes,[8] Charlson Comorbidity Index, age, sex, and mortality did not significantly differ in the 2 groups [adjusted hazard ratio (95% confidence interval) = 0.88 (0.40-1.92), $P = .7$]. Median duration of hospital stay did not significantly differ between the 2 groups [11 (7-16) vs 10 (7-19) days, $P = .8$]. Bacteremia during hospitalization was rare in both groups (5% vs 4%, $P = .9$). One case of *Clostridioides difficile* colitis was diagnosed in the antibiotics group.

In this observational study in older comorbid inpatients presenting severe forms of COVID-19, 1-month mortality was very high (nearly a third of patients) and did not appear to widely differ under

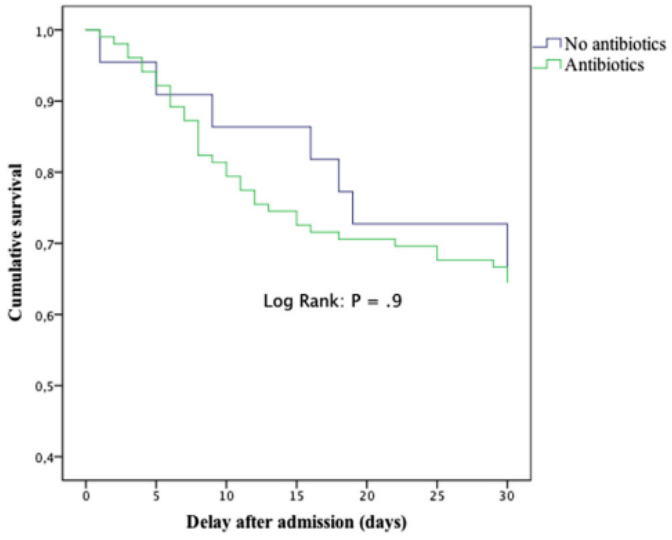

Fig. 1. One-month survival after admission for SARS-CoV-2 pneumonia in older patients with or without antibiotics.

The authors declare no conflicts of interest.

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antibiotic treatment. If confirmed, these preliminary results from a relatively small cohort of older inpatients with severe SARS-CoV-2 pneumonia suggest that the use of antimicrobial drugs should be restricted.

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Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2020.11.034.

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<u>Annexe 11:</u> Alessandra Marengoni, MD, PhD, Alberto Zucchelli, MD, Davide Liborio Vetrano, MD, PhD, Andrea Armellini, MD, Emanuele Botteri, MD, Franco Nicosia, MD, at al, ***Beyond Chronological Age: Frailty and Multimorbidity Predict In-Hospital Mortality in Patients With Coronavirus Disease 2019****,* The Journals of Gerontology: Series A*,*

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Research Article

Beyond Chronological Age: Frailty and Multimorbidity Predict In-Hospital Mortality in Patients With Coronavirus Disease 2019

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Abstract

Background: We evaluated whether frailty and multimorbidity predict in-hospital mortality in patients with COVID-19 beyond chronological age.

Method: A total of 165 patients admitted from March 8th to April 17th, 2020, with COVID-19 in an acute geriatric ward in Italy were included. Predisease frailty was assessed with the Clinical Frailty Scale (CFS). Multimorbidity was defined as the co-occurrence of ≥2 diseases in the same patient. The hazard ratio (HR) of in-hospital mortality as a function of CFS score and number of chronic diseases in the whole population and in those aged 70+ years were calculated.

Results: Among the 165 patients, 112 were discharged, 11 were transferred to intensive care units, and 42 died. Patients who died were older (81.0 vs 65.2 years, $p < .001$), more frequently multimorbid (97.6 vs 52.8%; $p < .001$), and more likely frail (37.5 vs 4.1%; $p < .001$). Less than 2.0% of patients without multimorbidity and frailty, 28% of those with multimorbidity only, and 75% of those with both multimorbidity and frailty died. Each unitary increment in the CFS was associated with a higher risk of in-hospital death in the whole sample (HR = 1.3; 95% CI = 1.05–1.62) and in patients aged 70+ years (HR = 1.29; 95% CI = 1.04–1.62), whereas the number of chronic diseases was not significantly associated with higher risk of death. The CFS addition to age and sex increased mortality prediction by 9.4% in those aged 70+ years.

Conclusions: Frailty identifies patients with COVID-19 at risk of in-hospital death independently of age. Multimorbidity contributes to prognosis because of the very low probability of death in its absence.

Keywords: COVID-19, Frailty, In-hospital mortality, Multimorbidity

Clinical manifestations of coronavirus disease 2019 (COVID-19) vary greatly ranging from asymptomatic infection to severe and sometimes fatal respiratory failure (1). Similar to other previously isolated coronaviruses responsible for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (2,3), severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) can cause interstitial pneumonia (4). The case-fatality rate has been reported to steeply increase with age worldwide, from 4.9% in the 0–59 years to 9.5% in the 60–69 years, reaching 25.2% in the 90+ year-old (5). In accordance with the Italian National Institute of Health surveillance system, persons who died by COVID-19 were more frequently older, males, and presented a mean number of 2.7 preexisting chronic diseases. Overall, 74% of the deceased individuals had multimorbidity (ie, 2 or more chronic diseases) (6). Hypertension, chronic obstructive pulmonary disease (COPD), malignancy, chronic kidney disease, cardiovascular disease, and diabetes mellitus were the most common comorbidities among hospitalized persons affected by COVID-19 (7), and patients with preexisting cardiovascular and metabolic conditions have the greatest risk of adverse outcomes (8).

Along with its burden on the health and well-being of affected individuals, the most severe cases of COVID-19 are currently overloading the health care systems of several countries, which are striving to adapt their actions to the new condition. A prompt and reliable identification of patients affected by COVID-19 at higher risk of death may direct clinical management and difficult decision making. Recommendations provided so far by health agencies suggest that patients' biological age—rather than chronological—must steer clinical decisions (9–11). However, instruments available to assess biological age are not yet ready for clinical applications. As a result, chronological age has been used in decision making, such as intensive care unit (ICU) admissions, without solid evidence supporting such decisions.

Frailty, a state of increased vulnerability caused by reduced homeostasis in several systems (12) and multimorbidity, the simultaneous presence of multiple chronic conditions in the same individuals (13), could be used as surrogate measures of biological aging, as they track the rate of decline in health and function with aging, and, independent of chronological age, their presence has been associated with a number of unfavorable outcomes including hospitalization, disability, and mortality (14–16). In the general population, as well as in individuals admitted to ICUs, the impact of frailty is clear even in persons without multimorbidity (17,18). Frailty predicts mortality in the adult population (19), is associated with lower probability of recovery in elderly persons hospitalized with influenza and acute respiratory illness (increasing the odd of death during the 30 days post-discharge) (20), and is a negative prognostic predictor in patients affected by HIV (21). Although frailty and multimorbidity can overlap, approximately one-fourth of persons with multimorbidity do not have frailty (22), suggesting that frailty and multimorbidity bring complementary information in the patients' assessment.

The aim of this study was to evaluate whether frailty and multimorbidity predict in-hospital mortality beyond chronological age among patients with COVID-19 admitted to a tertiary care hospital in Italy.

Method

Study Participants and Data Collection

This is a retrospective observational study including 171 consecutive patients with a diagnosis of COVID-19 admitted to the acute geriatric unit of the Civili Hospital in Montichiari (Brescia, Northern Italy) from March 8th to April 17th, 2020. At the onset of the COVID-19 emergency, the Montichiari hospital was designated as COVID-19 special hospital in the Lombardy region and the geriatric medicine unit of the hospital was open to both younger and older adults affected by the disease. Patients were admitted to the geriatric ward if they had signs or symptoms of COVID-19, independently of their age. Of the 171 patients, 6 were not included in this study due to a high amount of missing information in their medical charts. All the remaining 165 patients were followed up for the whole hospitalization in the acute geriatric ward.

By the 17th of April, all patients were either discharged (N = 112%–67.9%), transferred to the ICU (ICUs across the whole Lombardy or other regions) (N = 11%– 6.7%), or dead (N = 42–25.4%).

Patients were discharged if they displayed peripheral oxygen saturation >94% in ambient air, a respiratory frequency lower than 22 times per minute, and had no fever for 48 hours. The decision to discharge a patient was not affected by the paucity of resources, but always in keeping of the clinical conditions of the individual patient. The decision upon ICU transferal was made by critical care physicians, who evaluated the vital parameters, blood exams, and respiratory distress twice daily or upon request of the geriatric ward physician. Patients transferred to the ICU were younger (59.5 years, SD = 16.1); all of them were nonfrail, 5 (45.4%) had multimorbidity and the median number of drugs prescribed at home was 0 (IQR 3).

Nasal and pharyngeal swab samples were collected at hospital admission by trained nurses and total SARS-Cov-2 RNA was extracted for testing. COVID-19 cases were identified by reverse transcriptase-polymerase chain reaction (RT-PCR) assay for SARS-Cov-2 RNA. A small number of cases with a negative or undetermined test (N = 11) were considered to be infected by SARS-Cov-2 based on the computed tomography of the chest and the highly suggestive clinical characteristics (23). A recent systematic review of the literature showed that false-negative test results may occur in up to 20% to 67% of patients affected by COVID-19 (24).

The study was approved by the Ethical Committee of the Brescia County (Italy).

Data Collection

Information on age, sex, education, and living arrangement were collected. Education was categorized into primary (5 years of schooling or less) and secondary education (≥6 years). Clinical and laboratory characteristics and outcome data were obtained from medical records and anonymously aggregated. The following data were collected: smoking history, number of chronic diseases among a predefined and validated list of 60 diseases, (13) multimorbidity (defined as 2+ co-occurring diseases in the same patient), number of drugs before hospital admission, and symptoms and signs of infection (fever, cough, headache, dyspnea, weakness, ageusia, olfactory impairment, gastrointestinal problems).

Frailty was assessed at hospital admission by a geriatrician who collected information about the preinfection health status of the patient. Such information was collected directly from the patient if he/she was not cognitively impaired and affected by moderate disease. If the patient was cognitively impaired or severely ill, this information was collected from a proxy/caregiver. The Clinical Frailty Scale (CFS) was employed to assess frailty: the CFS is an ordinal 9-point scale in which the assessor makes decisions about the degree of frailty from clinical data (25). The

patients are scored from 1 "very fit" to 9 "terminally ill," with a score of 6 or more being indicative of moderate-to-severe frailty. According to the CFS, a patient is non- to mildly frail for scores <6 (1 being robust and physically active to 5 being dependent in instrumental activities of daily living such as shopping and managing medications), moderately frail from score 6 to 7 (6 being dependent in all the outdoor activities and bathing and 7 being dependent in personal care), and severely frail from scores 8 to 9 (8 being dependent in all basic activities of daily living and 9 being terminally ill). In the case of cognitive impairment or severe COVID-19 at admission, information regarding frailty was asked to a proxy/caregiver.

Laboratory data comprised of a complete blood count, white blood cells count, O_2, CO_2, pH blood gas test, and a C-reactive protein (CRP) test. Pharmacological treatments during hospitalization were prescribed in accordance with the Guidelines of the Lombardy section of the Italian Society of Infectious and Tropical diseases (26), and were informed by the patient's clinical features and availability of drugs.

Statistical Analysis

Data were described as count and proportion, mean and *SD*, or median and interquartile range, as appropriate. Differences in the characteristics between survived and deceased patients were assessed using a chi-squared test, Fisher's exact test, *t* test, or Mann–Whitney U test, as appropriate. In the Kaplan–Meier survival analysis and plot (Figure 1), the sample was stratified into 3 groups: nonfrail with 0 or 1 chronic conditions, nonfrail with multimorbidity, and frail with multimorbidity. In our sample, all the patients with frailty were also affected by multimorbidity. Cox proportional hazard regression models were employed to investigate the independent association of frailty (as CFS) and multimorbidity (as the count of chronic conditions) with survival. The analyses were run in the whole population and in the subsample of patients aged ≥70. In the survival analyses, the date of hospital admission was used as time 0. The date of discharge, ICU transferal, or death in the acute geriatric ward was used to set time of the right censoring or outcome. The proportional hazard assumption was satisfied in both cases (p for the Schoenfeld test against residuals for the analysis in the whole study population = .890 and among patients ≥70 years old = .900). The ROC curves (Figure 2) evaluate the accuracy in the prediction of mortality according to frailty and multimorbidity. Areas under the curve (AUC) were obtained through nonparametric ROC analyses and their 95% confidence intervals (95% CIs) were estimated by bootstrapping with replacement (N = 2000). Diagnostic tests reported in the table in Figure 2 were based on the cutoffs for moderate–severe frailty (CFS ≥ 6) and multimorbidity, tested in univariate analyses. C-statistics (Table 3) were obtained by calculating the AUCs of the values predicted by Cox proportional hazard models. Their 95% CIs and the comparison between models were estimated by bootstrapping with replacement (N = 2000). All analyses were conducted with R 3.6.3(27), with an alpha-level of .05.

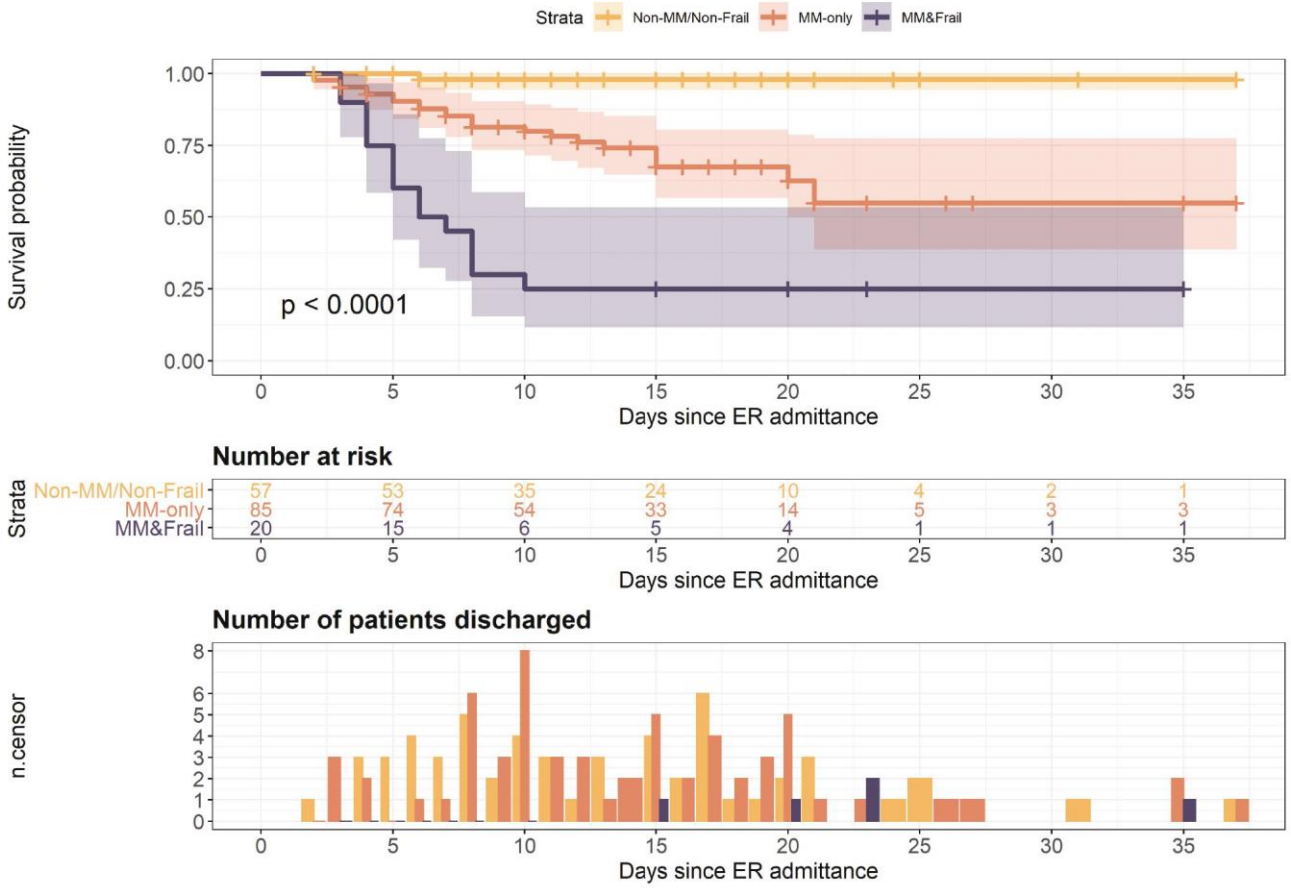
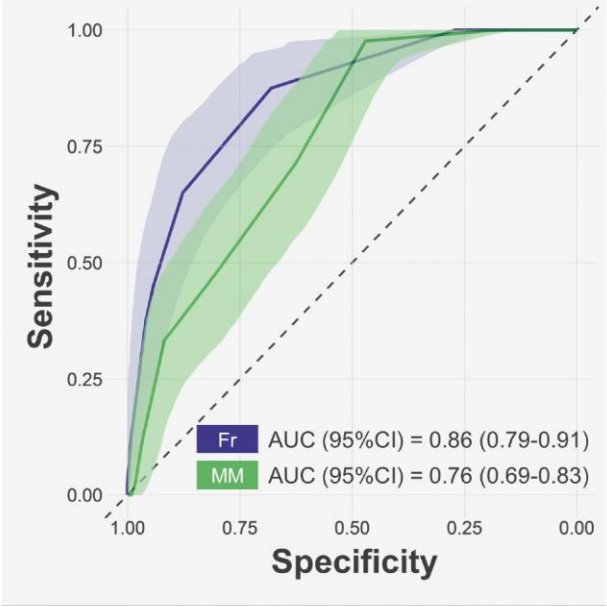


Figure 1. Kaplan–Meier curve for survival by multimorbidity (MM) and frailty combinations and discharge rate (frailty without multimorbidity was absent).



	Sens.	Spec.	PPV	NPV	LLR+	LLR-
CFS ≥ 6	0.38	0.96	0.75	0.82	9.15	0.65
2+ Chronic cond.	0.98	0.47	0.39	0.98	1.85	0.05

Figure 2. ROC curves for Clinical Frailty Scale (Fr) score and number of chronic conditions (MM) in the prediction of mortality. AUC and 95% confidence intervals (95% CIs) were estimated through bootstrapping (N = 2000). The table shows sensitivity (Sens.), specificity (Spec.), positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LLR+ and LLR–) for frailty (CFS ≥ 6) and multimorbidity (2+ chronic condition) in the prediction of mortality.

Results

As showed in Table 1, patients were 69.3 years old (*SD* 14.5) on average and 55.1% were 70 years or older; 60.6% were males and 49.7% had primary education. The median duration of symptoms before hospital admission was 7 days and the median length of hospital stay was 10 days (IQR 7–17). Overall, 28.5% of patients had an arterial oxygen saturation <90% at hospital admission. The median number of chronic diseases was 2 (IQR 1–4) and 64.2% of patients were affected by multimorbidity. The median CFS score was 2 (IQR 2–4) and 87.7% of patients had a CFS score <6. Patients who died were more likely to be older (p < .001) and had lower educational attainment (p = .001). The percentage of patients with arterial oxygen saturation <90% at hospital admission was 60.5% in those who died versus 17.0% in those who did not (p < .001). The median CRP was higher in those who died (p < .001). The median number of chronic coexisting diseases was higher among those who died (3 vs 2, p < .001). Thirty-seven percent of patients who died versus 4.1% of those who did not had a CFS score ≥6.

Tables 2 and 3 show Cox regression models reporting the hazard ratios (HRs) for death and the c-statistics derived from survival analyses associated with CFS score and number of chronic diseases adjusted for age, sex, and education in the whole sample and in patients aged 70+ years (N = 91), respectively. Each unit increase in CFS score was associated with increased in-hospital death both in the whole sample and among older individuals, whereas each unit increase in the number of chronic diseases was not significantly associated with higher risk of in-hospital mortality. The addition of the CFS improved the model's goodness of fit by 9.4% in the subsample of patients aged 70 years and older: the model containing CFS has a 9% increased probability to assign a higher risk of death to those who actually died during the hospitalization, in comparison to the model based on age, sex, and education only.

Figure 1 displays Kaplan–Meier survival plots for patients with no multimorbidity and no frailty as the reference group (n = 57 – median hospital length of stay = 11), those with multimorbidity only (n = 85 – median hospital length of stay = 11), and those with multimorbidity and frailty (n = 20 – median hospital length of stay = 6.5). In our study, frailty always co-occurred with multimorbidity. 1.8% of patients without multimorbidity and frailty, 28% of those with multimorbidity only, and 75% of those with both multimorbidity and frailty died during hospitalization.

The AUC for the prediction of in-hospital mortality was 0.86 (0.79–0.91) for the CFS and 0.76 (0.69–0.83) for the number of chronic diseases (Figure 2). The positive predictive value (PPV) of moderate-to-severe frailty (CFS ≥ 6) was 0.75 and the positive likelihood ratio was 9.15. The negative predictive value (NPV) of multimorbidity was 0.98 and the negative likelihood ratio was 0.05.

Discussion

In hospitalized patients with COVID-19, higher CFS scores were associated with mortality, independently of chronological age. Moreover, the CFS appeared to improve the prediction of death beyond chronological age among those aged 70+ years.

We used data collected during this emergency period to test the hypothesis that patients admitted to the hospital had some clinical characteristics that differentiated those who survived to the study's end from those who died. Studies in China have reported that patients with COVID-19 who suffered adverse outcomes were older than those who recovered, and that some specific chronic conditions were more prevalent in those who died (1,8,28,29). The findings of our study align with such previous reports, also adding new insight into the role of multimorbidity and frailty, independent of age as risk factors for mortality in those with COVID-19.

In our study, patients with CFS ≥ 6 were 9 times more likely to die during the hospitalization than those with lower scores. Of note, the CFS alone predicted in-hospital death with a discriminative ability of 88%. Currently, there is no internationally recognized standard definition and operationalization of frailty given its complex pathophysiology. The main reason for that is that the underlying mechanisms of frailty are still under investigation. At the same time, due to the urgency to have tool spendable in clinical practice, a high number of frailty definitions have been proposed in the last 2 decades, showing fair-to-good validity (30). We found that 12% of patients could be defined as moderately or severely frail, according to the CFS, which is the clinical tool suggested by the NICE guidelines for the assessment of older patients affected by COVID-19 infection (11). The CFS has shown a discriminative ability comparable to the Frailty Index (25) which is a model of accumulation of deficits, such as diseases and disability. Further, in patients admitted to a geriatric ward, the CFS and the Fried frailty phenotype (31) were equally suitable for differentiating between patients who died due to any cause from those who survived during follow-up (32). Compared to other frailty scales, the CFS has the specific strength that it has been validated as an adverse outcome

Table 1. Demographic and Clinical Characteristics of the Study Population in the Whole Sample and by Outcome

	Whole, *N* = 165	Survived, *N* = 123 (74.5)	Deceased, *N* = 42 (25.5)	*p*
Age, y, mean (*SD*)	69.3 (14.5)	65.2 (14.3)	81.0 (6.5)	<.001
<40 y	7 (4.2)	7 (5.7)	0 (0.0)	
40–49 y	16 (9.7)	16 (13.0)	0 (0.0)	
50–59 y	14 (8.5)	14 (11.4)	0 (0.0)	
60–69 y	37 (22.4)	34 (27.6)	3 (7.1)	
70–79 y	48 (29.1)	34 (27.6)	14 (33.3)	
80–89 y	38 (23.0)	17 (13.8)	21 (50.0)	
≥ 90 y	5 (3.0)	1 (0.8)	4 (9.5)	
Male sex	100 (60.6)	73 (59.3)	27 (64.3)	.702
Primary education	75 (49.7)	47 (41.6)	28 (73.7)	.001
Living alone	25 (18.2)	17 (16.5)	8 (23.5)	.507
Clinical Frailty Scale, median (IQR)	2.0 (2.0, 4.0)	2.0 (1.0, 3.0)	4.0 (3.0, 6.0)	<.001
Frailty (categorized)				<.001
No/mild frailty	142 (87.7)	117 (95.9)	25 (62.5)	
Moderate frailty	19 (11.7)	5 (4.1)	14 (35.0)	
Severe frailty	1 (0.6)	0 (0.0)	1 (2.5)	
Smoking habit				.363
No	74 (68.5)	62 (71.3)	12 (57.1)	
Ex/current	35 (31.5)	26 (28.7)	9 (42.9)	
Hypertension	98 (59.4)	67 (54.5)	31 (73.8)	.043
Type 2 diabetes mellitus	51 (30.9)	36 (29.3)	15 (35.7)	.557
Obesity/overweight	27 (16.4)	24 (19.5)	3 (7.1)	.089
Cognitive impairment	14 (8.5)	5 (4.1)	9 (21.4)	.002
Heart failure	5 (3.0)	3 (2.4)	2 (4.8)	.602
COPD	4 (2.4)	2 (1.6)	2 (4.8)	.268
Chronic diseases, median (IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	3.0 (2.0, 5.0)	<.001
Multimorbidity (2+ chronic conditions)	106 (64.2)	65 (52.8)	41 (97.6)	<.001
No. of drugs, mean (*SD*)	3.8 (3.2)	3.1 (3.2)	5.5 (2.4)	<.001
No. of days with symptoms before admission, median (IQR)	7.0 (5.0, 10.0)	7.0 (5.0, 10.0)	7.0 (4.0, 10.0)	.283
Length of hospital stay, days, median (IQR)	10.0 (7.0, 17.0)	13.0 (8.0, 18.0)	6.0 (4.0, 8.0)	<.001
COVID-19 clinical features				
Fever	147 (89.1)	110 (89.4)	37 (88.1)	1.000
Cough	83 (50.3)	64 (52.0)	19 (45.2)	.561
Dyspnea	70 (42.4)	51 (41.5)	19 (45.2)	.805
Gastrointestinal disturbances	31 (18.8)	27 (22.0)	4 (9.5)	.109
Headache	7 (4.2)	6 (4.9)	1 (2.4)	.680
Arterial oxygen saturation < 90%	41 (28.5)	18 (17.0)	23 (60.5)	<.001
Arterial oxygen concentration, mm Hg, median (IQR)	67.0 (53.5, 79.0)	69.0 (60.0, 81.5)	53.0 (42.7, 69.2)	<.001
White blood cells, 10^3/μL, median (IQR)	7.4 (5.8, 9.7)	6.8 (5.5, 8.9)	9.2 (6.4, 10.8)	.003
C-reactive protein, mg/L, median (IQR)	101.9 (51.1, 151.1)	86.6 (38.8, 140.0)	139.9 (91.8, 205.2)	.001

Note: COPD = chronic obstructive pulmonary disease; IQR = interquartile range. Missing: 14 for education, 28 for living situation, 3 for Clinical Frailty Scale and its categorization, 3 for number of days with symptoms, 14 for oxygen saturation and concentration, 8 for white blood cell count, and 8 for C-reactive protein.

predictor in hospitalized older people (33) but, on the other hand, it is strongly tangled with the presence of disability, especially for higher CFS scores. Finally, the CFS is timesaving, especially when applied by a trained physician such as a geriatrician. The latter characteristic was very important during the emergency of COVID-19. A recent scoping review showed that 5 out of 6 studies on frailty assessment in COVID-19 used the CFS to assess frailty (34). Subsequent to this review a large study mostly based on data from the UK was published showing that frailty measured by the CFS was strongly associated with mortality in hospitalized patients aged 61 years and older (35).

Central to the frailty concept is the multisystem involvement, including dysregulation of neuromuscular, endocrine, and immune systems. The age-related decline in immune function is well documented and it can contribute to frailty as well as to an increased susceptibility to acute and chronic diseases; aging and frailty lead to an imbalance between stressors and stress-buffering mechanisms that causes loss of compensatory reserve. In particular, changes in the innate immunity could enhance a proinflammatory state which is a fundamental component of frailty (36,37). In a systematic review of the literature, frailty and prefrailty were associated with higher inflammatory parameters, such as CRP, interleukin-6, elevated white blood cell, and fibrinogen levels (38). Further, in older adults, a reduced chemotaxis with an inefficient neutrophil migration may induced greater tissue damage and secondary systemic inflammation (39) that, among changes in T-cell function, may impair the overall immune response of the organism. Thus, in COVID-19, frailty is likely to be a good clinical marker of a substrate sensitive to infections, and to enhance the multiorgan involvement of the infection itself (40,41) as well as the dysregulated inflammatory response

Table 2. Multiadjusted Hazard Ratios (HRs) and 95% Confidence Intervals (95% CIs) of Death in All Patients

Model	Variables	HR (95% CI)	C-Statistic	% Difference With Model 1	*p* (absolute difference with Model 1)
1	Age	1.13 (1.08–1.18)	0.856	Ref.	Ref.
	Male sex	1.75 (0.86–3.53)			
	Primary education	1.47 (0.70–3.07)			
2	Age	1.12 (1.07–1.17)	0.857	+0.1%	.778
	Male sex	1.62 (0.79–3.33)			
	Primary education	1.34 (0.62–2.87)			
	Number of chronic conditions	1.07 (0.92–1.24)			
3	Age	1.10 (1.04–1.16)	0.888	+3.7%	.030
	Male sex	2.19 (1.05–4.58)			
	Primary education	1.40 (0.65–3.04)			
	CFS score	1.31 (1.05–1.62)			
4	Age	1.10 (1.04–1.16)	0.888	+3.7%	.042
	Male sex	2.11 (0.99–4.52)			
	Primary education	1.33 (0.58–3.04)			
	Number of chronic conditions	1.03 (0.87–1.22)			
	CFS score	1.30 (1.05–1.62)			

Note: CFS = Clinical Frailty Scale. The absolute difference between models was assessed through bootstrapping (N = 2000): p is shown. C-statics and absolute difference with Model 1; Model 1: age, sex, and education. Model 2: Model 1 + number of chronic conditions. Model 3: Model 1 + CFS score; Model 4: Model 1 + CFS score and number of chronic conditions. N at risk = 148, events = 36.

Table 3. Multiadjusted Hazard Ratios (HRs) and 95% Confidence Intervals (95% CIs) of Death in Patients Aged 70+Years (N = 91)

Model	Variables	HR (95% CI)	C-Statistic	% Difference With Model 1	*p* (absolute difference with Model 1)
1	Age	1.10 (1.04–1.17)	0.709	Ref.	Ref.
	Male sex	1.76 (0.85–3.67)			
	Primary education	1.51 (0.71–3.24)			
2	Age	1.10 (1.03–1.16)	0.704	−0.7%	.695
	Male sex	1.66 (0.79–3.51)			
	Primary education	1.40 (0.63–3.09)			
	Number of chronic diseases	1.06 (0.90–1.23)			
3	Age	1.08 (1.01–1.15)	0.776	+9.4%	.091
	Male sex	2.22 (1.03–4.78)			
	Primary education	1.45 (0.64–3.24)			
	CFS score	1.29 (1.04–1.62)			
4	Age	1.08 (1.00–1.15)	0.780	+10.0%	.086
	Male sex	2.17 (0.98–4.81)			
	Primary education	1.40 (0.59–3.33)			
	Number of chronic diseases	1.02 (0.86–1.21)			
	CFS score	1.29 (1.03–1.62)			

Note: CFS = Clinical Frailty Scale. The absolute difference between models was assessed through bootstrapping (N = 2000): p is shown. C-statics and absolute difference with Model 1; Model 1: age, sex, and education. Model 2: Model 1 + number of chronic conditions. Model 3: Model 1 + CFS score; Model 4: Model 1 + CFS score and number of chronic conditions. N at risk = 81, events = 34.

(1,42). All the reasons above may explain the strong association between frailty and mortality found in our and other studies. Whereas inflammatory dysregulation may well account for the link between frailty and COVID-19 mortality in older persons, other hypotheses may apply to middle-aged adults. In fact, frailty has a strong relationship with sarcopenia and malnutrition (36) which are not exclusive of older people and both conditions have been associated with poorer outcomes in adult affected by COVID-19 (43). However, due to the low number of deaths in people aged less than 65 years in this study, conclusions about the utility of the CFS in middle-aged persons cannot be drawn from our results and we cannot recommend its use in this part of the population.

Our study adds to the previous literature as we elucidated both the role of frailty measured by the CFS and multimorbidity. As demonstrated in an Italian case series by Onder et al., multimorbidity was found in 3 quarters of the individuals who died from COVID-19 (6). Indeed, the proportion of persons with multimorbidity increases with age (13), as well as the case-fatality rate of COVID-19, reported thus far (5). However, given the high prevalence of multimorbidity in the older population, this would not directly imply an effect of multimorbidity on poor prognosis in COVID-19. Interestingly, in our study, those without multimorbidity were 20 times more likely to survive during hospitalization than those affected by 2+ chronic diseases. In previous studies conducted in the community, it was estimated that about 1 quarter of persons affected by multimorbidity are not frail (22), suggesting that frailty and multimorbidity capture different aspects of health. Previous studies carried out before the COVID-19 pandemic showed that frailty indices and multimorbidity

have different accuracy in predicting mortality in older adults (44). Our findings on the different specificity and sensitivity of frailty and multimorbidity in predicting mortality in hospitalized patients with COVID-19 reinforce this assumption.

Identifying those who will require specific interventions early in the progression of the disease might help to avoid adverse outcomes. Moreover, the identification of those who are likely to recover without intensive care might be useful in planning resource allocation. This is particularly true in older patients; while chronological age is still used as a marker of health and a decision-making tool, there is strong evidence that frailty, multimorbidity, and other geriatric syndromes such as sarcopenia are better predictors of health-related outcomes in older patients (15,16,45). For example, decisions about specific treatments are still often based on chronological age and the presence of 1 or 2 chronic diseases, especially in the ICUs triage. Yet, literature indicates that "high-quality care cannot be accomplished by looking only at age and diagnoses" (46,47). In our study, patients who were transferred to the ICU were younger and nonfrail. Notably, the Italian Society of Anaesthesia, Analgesia and Intensive Care (SIAARTI) released some recommendations for exceptional resource-limited situations (48). Although the document mentions that "it might be needed to set an age limit for the admission to intensive care," it also suggests that "the presence of comorbidity and functional status must be carefully evaluated in addition to age." Our study suggests that frailty assessment should be considered.

Limitations

First, data were collected retrospectively using medical charts and electronic records and a complete comprehensive assessment of patients was not performed. Future studies should include a multidimensional evaluation including the assessment of predisease mobility, functional and cognitive abilities, and the availability of social support. Indeed, despite the CFS is a scale widely used as a measure of frailty, it is mainly based on a functional evaluation and, as such, it may partially describe some aspects of the disability process. Thus, other frailty tools based on more objective measures should be tested in the future in order to confirm our findings. Secondly, we cannot exclude that during the severe and unexpected public health emergency, the most severely frail older patients were not even admitted to hospitals (in our sample, the percentage of patients with moderate-to-severe frailty was 12%). Under this assumption, our results are underestimating the strength of the association, but this hypothesis should be tested in future studies. Third, we were not able to retrieve the vital status of patients transferred to the ICU, because patients needed of intensive care were transferred to other hospitals within the same or to other regions according to the availability of resources. However, sensitivity analyses, first excluding patients transferred to the ICU, and second treating transferred patients as deaths, led to comparable results. Fourth, CFS intra- or interobserver variability was not evaluated due to limited time and resources. Fifth, the aim of our study was to investigate only in-hospital mortality and we lack data about early mortality after discharge. So, we cannot exclude the possibility that some patients may have died right after the discharge. Lastly, during the emergency, blood samples were not stored and, thus, they are not available for future analyses of biomarkers of interest, as for example inflammatory cytokines.

On the other hand, the major strengths of the study are the few missing data and the novelty of the clinical characteristics analyzed; despite the small sample size, the results are robust.

Conclusions

Our findings indicated that frailty was independently associated with mortality in patients affected by COVID-19 and added prognostic information beyond chronological age in those aged 70 years or older. Furthermore, the absence of multimorbidity appeared to be a relevant positive prognostic feature. Assessing for frailty and multimorbidity and embedding these 2 conditions in the decision-making process and clinical management of COVID-19 patients should be considered.

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Conflict of Interest

None declared.

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Author Contributions

A.M. designed the study, had full access to all data, and takes responsibility for the accuracy and integrity of the data analysis. A.Z. and D.L.V. analyzed the data and contributed to the interpretation, literature search, and writing of the manuscript. A.M., F.N., A.A., E.B., E.G., A.B., and P.G. contributed to data collection and interpretation. L.Fe., L.Fr., R.B., and G.O. critically revised the analyses and the interpretation of the findings and contributed to writing of the manuscript. All the co-authors reviewed the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. A.M. is the guarantor.

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Annexe 12 : Girard N, Odille G, Sanchez S, Lelarge S, Mignot A, Putot S, et al. ***Comment on: "Beyond Chronological Age: Frailty and Multimorbidity Predict In-hospital Mortality in Patients With Coronavirus Disease 2019".*** *The Journals of Gerontology: Series A.*

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OXFORD

Letter to the Editor

Comment on: "Beyond Chronological Age: Frailty and Multimorbidity Predict In-hospital Mortality in Patients With Coronavirus Disease 2019"

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Dear Editor,

We read with great interest the article by Alessandra Marengoni et al., evaluating whether frailty and multimorbidity predict in-hospital mortality in patients with COVID-19 beyond chronological age (1). This interesting question has been on the mind of every physician providing acute medical care to older COVID-19 patients during what has been the most deadly outbreak in the world since Spanish Influenza in 1918. Compared with younger patients, older patients are disproportionately affected and at a much higher risk of mortality: The fatality rate is evaluated at up to 30% in patients aged over 80 years compared with up to 5% in the population as a whole (2). Previous observational studies report that older age and comorbidities are associated with a higher rate of mortality (3–7).

However, whether older age is an independent predictor of in hospital mortality after careful adjustment on comorbidities and frailty remains a matter of debate. As highlighted by Marengoni et al., the frequent use of chronological age in decision-making for questions that may include access to intensive care, poses serious ethical problems in the absence of solid evidence in support of such decisions (8). From their observational data on 165 hospitalized patients, the authors conclude that frailty and multimorbidity are independent predictors of mortality and should therefore be assessed, and not only chronological age. They consider that these 2 conditions are worth embedding in the decision-making process for COVID-19 patients.

In this context, observational studies assessing the respective prognostic weight of comorbidities, frailty, and age in geriatric setting are particularly welcome. Notably, Mendes et al. recently reported interesting results confirming these conclusions (9): In 235 patients hospitalized with COVID-19 with a mean age of 86 years, frailty, comorbidities, and functional status, but not age per se, were independent risk factors for mortality.

In a multicenter observational study of patients aged > 75 years in COVID-19 geriatric units of 4 hospitals in Burgundy, one of the most affected regions in France, we sought to confirm such findings. We therefore included all consecutive patients aged > 75 years and hospitalized for COVID-19 (with positive RT-PCR test). Clinical presentation, comorbidities, and dependence were recorded at admission. The World Health Organization (WHO) severity score was evaluated at admission according to current guidelines (10). Factors associated with 1-month mortality were evaluated in univariate and multivariate analyses using a Cox regression model. This study was approved by the local ethics committee.

We included 142 consecutive patients with a median age of 86 years, and each patient was followed up for 1 month after admission. Overall, 48 (33.8%) patients had died by the end of follow-up. As shown in Table 1, after adjustment on other prognostic factors, older age remained scarcely associated with 1-month mortality (adjusted hazard ratio [95% confidence interval]: HR = 1.07 [1.00–1.14]), whereas male sex (HR = 2.21 [1.00–4.88]) and high Charlson Comorbidity Index scores (HR = 1.16 [1.02–1.30]) were independently associated with a worse prognosis. Dependence, however, was not significantly associated with short-term prognosis. Concerning clinical parameters at admission with prognostic value, heart rate (HR = 1.02 [1.00–1.04]), and WHO severity score (HR = 2.23 [1.31–3.80]) remained strongly associated with poorer outcomes.

Table 1. Parameters at Admission Associated With 1-Month Mortality in Older COVID-19 Inpatients (*n* [%] or median [interquartile range])

	Alive *n* = 95	Dead *n* = 48	*p* Value (univariate analysis)	Adjusted HR (multivariate analysis)
Age (years)	86 [81–89]	87 [83–91]	.12	1.07 (1.00–1.14)*
Men	44 (46)	31 (65)	.04	2.21 (1.00–4.88)*
Body mass index (kg/m²)	24 [21–27]	25 [21–28]	.79	
Acquisition site				
Community	67 (70)	31 (65)	.47	
Nursing home	27 (28)	15 (31)	.72	
Hospital	17 (18)	16 (33)	.04	
Dependence				
Walk alone	40 (42)	18 (37)	.37	
Walk with help	47 (49)	22 (46)	.15	
Bedridden	8 (8)	8 (17)	.14	
ADL scale < 3	16 (17)	11 (23)	.38	
Comorbidities				
Chronic heart failure	19 (20)	13 (27)	.34	
Myocardial infarction	18 (19)	8 (17)	.78	
Cerebrovascular disease	26 (27)	20 (42)	.08	
Neurocognitive disorders	38 (40)	26 (54)	.11	
Chronic lung disease	17 (18)	2 (4)	.02	
Diabetes	20 (21)	10 (21)	.96	
Chronic liver disease	2 (4)	5 (8)	.04	
Chronic kidney disease	10 (10)	13 (27)	.01	
Cancer	20 (21)	14 (29)	.28	
Charlson Index	2 [1–4]	3 [2–5]	.001	1.16 (1.02–1.30)*
Clinical parameters				
Heart rate (/min)	77 [69–87]	85 [73–99]	.005	1.02 (1.00–1.04)*
SBP (mmHg)	134 [118–150]	132 [114–145]	.37	
DBP (mmHg)	69 [59–78]	70 [61–82]	.43	
Temperature (°C)	37.2 [36.7–37.8]	37.3 [36.5–37.8]	.91	
Respiratory rate (/min)	30 [22–32]	30 [23–32]	.41	
WHO COVID-19 score	2 [2–3]	3 [2–3]	<.001	2.23 (1.31–3.80)*

Note: ADL = Activity of daily living; DBP = Diastolic blood pressure; SBP = Systolic blood pressure; WHO COVID-19 score = World Health Organization COVID-19 severity score, (10).

*$p < .05$.

In conclusion, these findings support Marengoni's proposal that comorbidities should be considered in the decision-making process for older COVID-19 patients more than chronological age alone. Moreover, the short-term prognosis is above all driven by the acute clinical presentation, even in frail older adults.

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<u>Annexe 13:</u> Marcello Covino, Giuseppe De Matteis, Maria Livia Burzo, Francesco Franceschi, Claudio Sandroni, ***Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores****, Journal of the American Geriatrics Soc*

Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores

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BACKGROUND/OBJECTIVES: Several scoring systems have been specifically developed for risk stratification in COVID-19 patients.

DESIGN: We compared, in a cohort of confirmed COVID-19 older patients, three specifically developed scores with a previously established early warning score. Main endpoint was all causes in-hospital death.

SETTING: This is a single-center, retrospective observational study, conducted in the Emergency Department (ED) of an urban teaching hospital, referral center for COVID-19.

PARTICIPANTS: We reviewed the clinical records of the confirmed COVID-19 patients aged 60 years or more consecutively admitted to our ED over a 6-week period (March 1st to April 15th, 2020). A total of 210 patients, aged between 60 and 98 years were included in the study cohort.

MEASUREMENTS: International Severe Acute Respiratory Infection Consortium Clinical Characterization Protocol-Coronavirus Clinical Characterization Consortium (ISARIC-4C) score, COVID-GRAM Critical Illness Risk Score (COVID-GRAM), quick COVID-19 Severity Index (qCSI), National Early Warning Score (NEWS).

RESULTS: Median age was 74 (67–82) and 133 (63.3%) were males. Globally, 42 patients (20.0%) deceased. All the score evaluated showed a fairly good predictive value with respect to in-hospital death. The ISARIC-4C score had the highest area under ROC curve (AUROC) 0.799 (0.738–0.851), followed by the COVID-GRAM 0.785 (0.723–0.838), NEWS 0.764 (0.700–0.819), and qCSI 0.749 (0.685–0.806). However, these differences were not statistical significant.

CONCLUSION: Among the evaluated scores, the ISARIC-4C and the COVID-GRAM, calculated at ED admission, had the best performance, although the qCSI had similar efficacy by evaluating only three items. However, the NEWS, already widely validated in clinical practice, had a similar performance and could be appropriate for older patients with COVID-19. **J Am Geriatr Soc 69:37-43, 2021.**

Keywords: COVID-19; NEWS; COVID-GRAM; ISARIC-4C; qCSI

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INTRODUCTION

The novel coronavirus designated SARS-CoV-2, has determined an international outbreak of respiratory illness named COVID-19.[1,2] Older adults and patients with previous comorbid conditions are at higher risk of developing severe disease, and death.[3-5]

The prevalence of hypoxic respiratory failure in patients hospitalized with COVID-19 was estimated to be about 19%, with up to 12% of patients requiring mechanical ventilation.[1-2,4] Indeed, based on available data, from 5% to 10% among hospitalized patients will require ICU admission, with rates even higher in older patients.[5-8]

In this context of critically ill patients' overflow, it is mandatory to establish clear and objective criteria to

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stratify COVID-19 risk for death. To date, already available national early warning scores (NEWS), and specifically developed clinical rules and scores, have been proposed for risk stratification in COVID-19 patients.[9-13] Currently, even though most of developed scores include age among the factors evaluated for risk prediction, none of these tools was validated in a geriatric population, which indeed carries the highest risk of worse outcome in COVID-19.

The aim of this study is to evaluate, in older patients with COVID-19, the performance for death risk stratification of specifically developed scoring systems, including the International Severe Acute Respiratory Infection Consortium Clinical Characterization Protocol-Coronavirus Clinical Characterization Consortium (ISARIC-4C) score, the COVID-GRAM Critical Illness Risk Score (COVID-GRAM), the quick COVID-19 Severity Index (qCSI).[11-13] These specifically developed scores were compared with the widely validated NEWS risk score.[14]

METHODS

Study Design

This is a single-center, retrospective observational study, conducted in the ED of an urban teaching hospital, which is a referral center for COVID-19, in central Italy.

We reviewed the clinical records of all the patients 60 years or more old consecutively admitted to our ED over a six-week period (from March 1st to April 15th, 2020). COVID-19 was diagnosed on the basis of the WHO interim guidance. We included in the analysis only patients with positive result on real-time reverse-transcriptase–polymerase-chain-reaction assay of nasal and pharyngeal swab specimens.[15]

We excluded patients already on orotracheal intubation at ED arrival, and patients for whom a do not resuscitate order was in place.

Study Variables

The following information were extracted from computerized clinical records: age, sex, clinical presentation symptoms, temperature, heart rate (HR), respiratory rate (RR), blood pressure (BP), Glasgow Coma Scale (GCS) score, oxygen supplementation, peripheral oxygen saturation (SpO_2), laboratory values, radiographic imaging, and clinical history. Physiological parameters were assessed at ED admission. Comorbidities were evaluated according to Charlson comorbidity index.[16]

Early Warning Scores for COVID-19 Risk Stratification

Four early warning scores were evaluated: three were specifically developed for COVID-19 (ISARIC-4c, COVID-GRAM, qCSI), while the NEWS score was recently validated in this setting.[11-14] The qCSI assesses the respiratory function; the COVID-GRAM, the ISARIC 4C, and the NEWS also include the assessment of cardiovascular function, level of consciousness, age, number of comorbidities, and a selection of laboratory tests (Supplementary Table S1).

All the parameters evaluated for scores calculation were obtained from ED electronic records.

Study Endpoint

The primary study endpoint was all-causes in hospital death.

Statistical Analysis

Continuous variables are reported as median (interquartile range), and are compared at univariate analysis by Mann–Whitney *U* test. Categorical variables are reported as absolute number (percentage), and are compared by chi-square test (with Fisher's test if appropriate).

For patients with incomplete dataset of parameters to calculate the scores (either vital parameters or laboratory values), we utilized a data imputation by using a multiple imputation approach.[17] We excluded patients with three or more parameters missing, since the effect on final scores calculation would have been highly unpredictable. The missing parameters were imputed by using a multiple regression model including the available parameters in the dataset, the triage code at ED admission, and patient age. The limit of imputed parameters was set according to each parameter range in the study cohort.

Once the selected scores were calculated for each patient, receiver operating characteristic (ROC) curve analysis was used to evaluate the overall performance in predicting the defined adverse outcome. Youden's index was used to estimate optimal cutoff points and corresponding sensitivity and specificity at selected score threshold values. The comparison between the ROC AUCs was made according to DeLong method.[18]

A two sided *P* value .05 or less was regarded as significant. Data were analyzed by SPSS v25® (IBM, IL).

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and its later amendments, and was approved by the local Institutional Review Board (IRB #001705520).

RESULTS

A total of 210 patients, aged between 60 and 98 years met the inclusion criteria and were included in the study cohort (Supplementary Figure S1). Median age was 74 (67–82) and 133 (63.3%) were males (Table 1).

Globally, 42 patients (20.0%) deceased (Table 1). When compared with survived patients, we found that deceased patients were significantly older (81 (74–85) vs 72 (66–80); $P < .001$), had worse radiological findings, and had a higher number of comorbidities (Charlson comorbidity index 5 (4–6) vs 4 (3–5); $P < .001$) (Table 1). In particular, deceased patients had a higher rate of dementia (17.5% vs 2.2%, $P < .001$), and a higher rate of renal disease (33.3% vs 7.7%, $P < .001$).

Among vital parameters at admission SpO_2, respiratory rate and heart rate were significantly worse in deceased patients, whereas the two groups had similar admission values in term of temperature and blood pressure (Table 1).

Table 1. Demographic and Clinical Characteristics of Enrolled Patients

Variable	All Population n = 210	Survived n = 168	Deceased n = 42	P
Age	74 (67–82)	72 (66–80)	81 (74–85)	<.001
Sex (male)	133 (63.3)	106 (63.1)	27 (64.3)	.886
Physiological parameters at ED presentation				
Peripheral oxygen saturation (%)	94 (90–96)	94 (92–96)	89 (80–92)	<.001
Respiratory rate (breaths/min)	18 (16–20)	18 (15–20)	19 (16–22)	.032
Heart rate (beats/min)	84 (72–99)	82 (71–95)	89 (76–110)	.011
Systolic blood pressure (mmHg)	130 (114–140)	129 (113–141)	128 (111–135)	.790
Diastolic blood pressure (mmHg)	78 (66–86)	78 (70–87)	73 (65–84)	.404
Axillary temperature (°C)	36.6 (36.0–37.5)	36.5 (36.1–37.3)	37.2 (36.2–38.2)	.711
Radiological findings				
Negative	27 (12.9)	26 (15.5)	1 (2.4)	
Interstitial/monolateral	110 (52.3)	101 (60.1)	9 (21.4)	<.001
Bilateral pneumonia	73 (34.8)	41 (24.4)	32 (76.2)	
Comorbidities				
Charlson comorbidity index	4 (3–5)	4 (3–5)	5 (4–6)	<.001
Hypertension	120 (57.1)	92 (54.8)	28 (66.7)	.163
Obesity	4 (1.9)	3 (1.8)	1 (2.4)	1.000
Coronary artery disease	45 (21.4)	38 (22.6)	7 (16.7)	.400
Congestive heart failure	39 (18.6)	30 (17.9)	9 (21.4)	.594
Diabetes mellitus	27 (12.9)	23 (13.7)	4 (9.5)	.471
Dementia	10 (5.7)	3 (2.2)	7 (17.5)	<.001
COPD	19 (9.0)	13 (7.7)	6 (14.3)	.186
Renal disease	27 (12.9)	13 (7.7)	14 (33.3)	<.001
Malignancy	15 (7.1)	12 (7.1)	3 (7.1)	1.000
Laboratory values				
Hemoglobin (g/dl)	12.7 (9.0–14.3)	12.9 (9.0–14.2)	12.4 (9.1–14.5)	.953
Neutrophil (cells/mm^3)	4,890 (3,570–6,930)	4,690 (3,540–6,610)	5,930 (3,715–8,935)	.019
Lymphocyte (cells/mm^3)	940 (670–1,290)	950 (695–1,280)	825 (570–1,600)	.591
Neutrophil/lymphocyte ratio	5.3 (3.3–8.1)	5.1 (3.2–7.6)	6.5 (3.9–12.2)	.026
Creatinine (mg/dl)	0.98 (0.78–1.42)	0.96 (0.75–1.27)	1.45 (0.88–2.05)	.003
Blood urea nitrogen (mg/dl)	20 (16–33)	19 (15–25)	37 (20–58)	<.001
Sodium (mEq/L)	138 (135–140)	138 (135–140)	138 (134–141)	.692
Lactate dehydrogenase (UI/L)	324 (241–440)	306 (233–412)	511 (314–801)	<.001
Alanina transpherase (UI/L)	19 (13.5–32.5)	18.5 (13–30.5)	21 (15–46)	.248
Direct bilirubin (mg/dl)	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.6 (0.4–1.0)	.725
C-reactive protein (mg/L)	66.8 (28.1–141.0)	53.1 (25.7–105.6)	145 (77.9–210.5)	<.001
Prothrombin time (s)	11.2 (10.7–11.9)	11.2 (10.6–11.8)	11.4 (10.8–12.4)	.220
Fibrinogen (mg/dl)	478 (392–580)	465 (390–550)	512 (405–703)	.088
D-dimer (ng/ml)	1,230 (709–3,359)	1,228 (619–2,771)	2,071 (900–5,412)	.194
Risk scores				
NEWS	3 (2–6)	3 (1–5)	6 (3–9)	<.001
ISARIC 4C	9 (7–10)	8 (6–10)	11 (9–12)	<.001
COVID-GRAM	17.3 (8.5–34.4)	13.9 (7.1–26.9)	38.1 (23.8–56.8)	<.001
qCSI	4 (0–6)	2 (0–5)	7 (4–10)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-GRAM, COVID-Gram Critical Illness Risk Score; ISARIC-4C, International Severe Acute Respiratory Infection Consortium Clinical Characterization Protocol-Coronavirus Clinical Characterization Consortium; NEWS, national early warning score; qCSI, quick COVID severity index.

Laboratory values at admission associated to death were higher C-reactive protein (CRP), blood urea nitrogen, LDH, absolute neutrophil count, and neutrophil/lymphocyte ratio (Table 1).

All the four scores evaluated showed a fairly good predictive value with respect to in-hospital death. The ISARIC-4C score had the highest area under ROC curve (AUROC) 0.799 (0.738–0.851), followed by the COVID-GRAM 0.785 (0.723–0.838), NEWS 0.764 (0.700–0.819), and qCSI 0.749 (0.685–0.806) (Figure 1). However, these differences were not statistically significant.

When comparing score sensitivity, COVID-GRAM and ISARIC-4C had the best performance, both reaching 88.1% sensitivity for COVID-GRAM greater than 17.7 and ISARIC-4C greater than 8 (Table 2). However, COVID-GRAM had a slightly higher negative predictive value (Table 2). The qCSI had the best specificity, thus having a qCSI greater than 5 the highest positive predictive value for

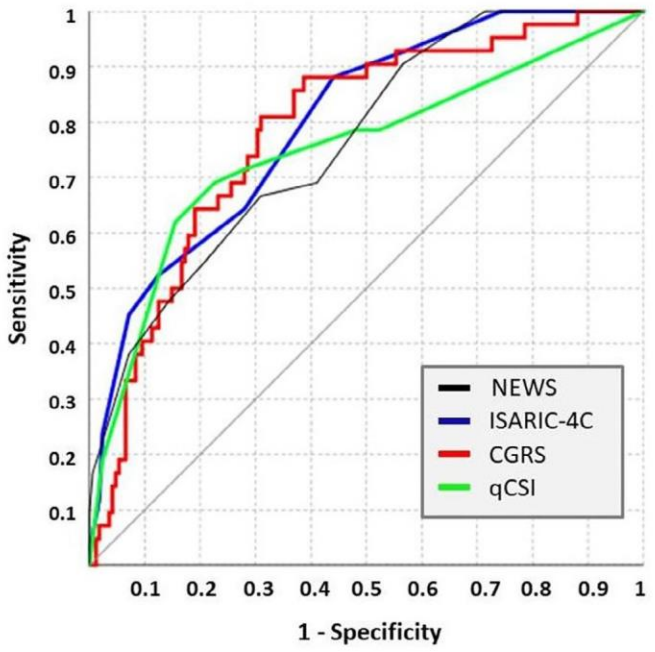

Figure 1. Graphical representation of the receiver operating characteristic (ROC) curve of the evaluated score.

death (43.3 (35.1–51.9)) (Table 2). The worst performer in this group was the NEWS, still keeping a fair negative predictive value of 89.2 (84.2–92.8) at selected cutoff.

DISCUSSION

The main result of present study is that among COVID-19 older patients the specifically developed scores ISARIC-4C, COVID-GRAM, and qCSI, although slightly superior in terms of overall AUROC and sensitivity, do not perform significantly better than the standard NEWS. However, the qCSI gave the best results in terms of specificity by evaluating only three parameters.

The SARS-CoV-2 primarily infects the upper respiratory and gastrointestinal tracts,[19] binding to human angiotensin-converting enzyme 2 for cell entry.[1,2,4,5,20] Severe hypoxia and respiratory distress are common features of COVID-19, and septic shock occurs mainly as a result of end-stage organ failure.[1,2,5] Radiological findings confirm the extensive lung involvement, and up to 98% of symptomatic patients show bilateral ground glass opacity, and multiple lobular and subsegmental consolidation areas at chest imaging.[20]

The results of the present study are largely explained by both the underlying pathophysiological mechanisms and the clinical presentation of COVID-19. Indeed, since the acute hypoxia is the main determinant of disease progression and severity, the evaluation of respiratory function is crucial for score prediction ability.

All the evaluated scores include an assessment of respiratory function, even if obtained in different ways. The NEWS includes both the SpO_2 and the respiratory rate in the calculation, as well as the ISARC-4C and the qCSI. For the COVID-GRAM calculation, the respiratory function is indirectly derivated by the assessment of X-ray abnormalities, and directly evaluated as the presence of dyspnea, as

Table 2. Sensitivities, Specificities, Negative and Positive Predictive Values, Positive and Negative Likelihood Ratios for NEWS, COVID-GRAM, ISARIC-4C, and qCSI Scoring Systems for Predicting Death of COVID-19 Older Patients

Score	ROC AUC	Cut off value	Sensitivity (%)	Specificity (%)	+LR	−LR	PPV	NPV
NEWS	0.764 (0.700–0.819)	>4	66.7 (50.5–80.4)	69.0 (61.5–75.9)	2.1 (1.6–2.9)	0.5 (0.3–0.7)	35.0 (28.3–42.4)	89.2 (84.2–92.8)
COVID-GRAM	0.785 (0.723–0.838)	>17.7	88.1 (74.4–96.0)	61.3 (53.5–68.7)	2.3 (1.8–2.8)	0.2 (0.1–0.4)	36.3 (31.3–41.5)	95.4 (90.0–97.9)
ISARIC-4C	0.799 (0.738–0.851)	>8	88.1 (74.4–96.0)	55.9 (48.1–63.6)	2.0 (1.6–2.5)	0.2 (0.1–0.5)	33.3 (29.0–38.0)	94.9 (89.1–97.7)
qCSI	0.749 (0.685–0.806)	>5	69.0 (52.9–82.4)	77.4 (70.3–83.5)	3.0 (2.2–4.3)	0.4 (0.3–0.6)	43.3 (35.1–51.9)	90.9 (86.3–94.1)

Note: Optimal cutoff was chosen according to Youden index J. Differences among area under ROC curves did not reach statistical significance.

Abbreviations: NEWS, National early warning score; COVID-GRAM, COVID-Gram Critical Illness Risk Score; ISARIC-4C, International Severe Acute Respiratory Infection Consortium Clinical Characterization Protocol-Coronavirus Clinical Characterization Consortium; qCSI, quick COVID severity index; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, Positive predictive value.

reported by the patient. The qCSI and the NEWS both evaluate the supplemental oxygen flow given to patients, although this latter measure has a high variability, being not always directly linked to effective patient's respiratory distress.

Apart from qCSI that evaluate only respiratory distress, all the scores evaluate neurological status, by using a simplified version of GCS (normal or <15 for ISARIC-4C), the Alert, Verbal, Pain, Unresponsive (AVPU) scale (for NEWS), and simply conscious/unconscious for COVID-GRAM. However, although neurologic involvement is common in COVID-19, a severe depression of consciousness is rare.[21] Indeed, in our cohort only seven (3.3%) patients presented with GCS less than 15 at admission, and three (1.4%) were unconscious. Hence, the contribution of this item to the score prediction was low.

The relatively low incidence of shock in COVID-19[1,2] could explain why the blood pressure in ED did not seem to be associated to worse outcome (Table 1) in our population. Indeed, none of the specifically designed scores for COVID-19 evaluates blood pressure.

Both COVID-GRAM and ISARIC 4C evaluate patients comorbidities. While the latter utilizes the Charlson Index adding obesity,[22] the COVID-GRAM evaluates a selected number of conditions, including hypertension and hepatitis B. As our study was conducted in a population of COVID-19 older patients, most of them presenting comorbidities, the influence of this item was reduced for the overall prediction. Nevertheless, our data confirmed that deceased patients showed an overall higher Charlson comorbidity index, but dementia and renal disease were significantly higher. Indeed, COVID-19 patients with cognitive impairment are at high risk of worse outcome, and this is a major challenge in geriatric populations.[6,23,24]

Among the scores we assessed, ISARIC-4C and COVID-GRAM include laboratory tests in their model. ISARIC-4C includes blood urea nitrogen and CRP, whereas COVID-GRAM include lactate dehydrogenase (LDH) and direct bilirubin. CRP and LDH were already described to be associated to advanced pulmonary disease in COVID-19,[25,26] as well as kidney damage and increased blood urea nitrogen,[27] as confirmed in our study. Conversely, we cannot confirm the usefulness of bilirubin evaluation since the hepatic involvement in our cohort was limited.

Both the COVID-GRAM and the ISARIC-4C assign an increased risk value for older age. However, in our selected population of patients above 60 years the weight of age was probably reduced because of the limited age range. This may partly explain why the PPV for hospital mortality of both COVID-GRAM and ISARIC-4C was lower than in the original reports.[11,13] Among the scores we tested, qCSI had the highest PPV for predicting hospital mortality (43.3% for qCSI > 5). The most likely reason is that qCSI is focused on respiratory failure, which is the major cause of death in COVID-19 patients. Despite the AUROC of qCSI was the lowest among the scores we tested in our study, this score may be preferred for a quick bedside detection of patients at higher risk of adverse events. In fact, qCSI requires only three clinical parameters (respiratory rate, pulse oximetry, and oxygen flow rate). Conversely, despite the higher complexity and the need of laboratory tests, ISARIC-4C and COVID-GRAM showed a high NPV (95%) and, as such, they can be used to exclude the risk of subsequent deterioration in patients destined to a non-critical area.

Finally, only ISARIC-4C considers the gender in risk prediction. Nonetheless, although male sex was associated to worse outcome in several reports,[3-5] patient gender was not significantly associated to a different outcome in our population (Table 1).

Study Limitations

As for any retrospective study some limitations are worth considering. First, our sample size is limited and therefore, the global accuracy of our ROC curve estimation could be reduced, still keeping a good reliability in ROC curve comparison. Moreover, we did not collect data about total time of eventual O_2 supplementation before ED admission, and this could affect the SpO_2 measurement at ED arrival.

Conclusions

Among the evaluated scores, the ISARIC-4C and the COVID-GRAM, calculated at ED admission, had the best performance in predicting death in COVID-19 older patients. Moreover, the qCSI, although not specifically designed for death risk prediction had similar efficacy by evaluating only three items, being the best choice for a quick assessment. However, the longtime validated NEWS had a similar performance and, since it represents the standard early warning score in many institutions, could be appropriate also for older patients with COVID-19.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Flow-chart of the cohort selection for the study.

Supplementary Table S1: Early warning scores for COVID-19 risk stratification.

<u>Annexe 14 :</u> Odille G, Girard N, Sanchez S, Lelarge S, Mignot A, Putot S, et al. ***Comment on: Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores****. Journal of the American Geriatrics Soc*

Comment on: Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores

To the Editor: We read with interest the article by Marcello Covino et al,[1] who evaluated the prognostic performance of four prognostic scores in 210 confirmed COVID-19 patients aged 60 years or more hospitalized via the Emergency Department. They found that all four scores had a good predictive value for in-hospital death: the ISARIC-4C score[2] had the highest area under receiver operating characteristic curve (AUROC) 0.80 (0.74–0.85), followed by the COVID-GRAM 0.78 (0.72–0.84),[3] NEWS 0.76 (0.70–0.82),[4] and quick COVID-19 severity index (qCSI) 0.75 (0.68–0.81).[5]

Given the burden of the pandemic in older population, we applaud the authors for specifically evaluating these new scores in older patients. However, despite the interest of such scores for predicting short-term outcomes and helping physicians provide adequate medical care, we are afraid that their relative complexity could hinder their use in difficult contexts, especially in nursing-homes and primary care. On that point, we agree with the authors that the easy-to-use qCSI, which uses three every-day clinical measures, is of particular interest.

As underscored by the authors, short-term prognosis is mainly driven by respiratory state, even in older patients. Additionally, the best prognostic scores mainly explore respiratory function, which is mostly clinically evaluated by bedside parameters. The World Health Organization (WHO) propose an easy-to-use severity scale in their COVID-19 clinical guidance, based solely on respiratory evaluation (S1: no pneumonia; S2: pneumonia, with SpO2 ≥ 90% on room air; S3: severe pneumonia, with respiratory rate > 30 breaths/min or SpO2 < 90% on room air; S4: critical disease, with acute respiratory distress syndrome).[6] To our knowledge, this pragmatic scale has not yet been evaluated in a geriatric setting.

In a multicenter observational study of patients aged more than 75 in COVID-19 geriatric units of four French hospitals, we sought to evaluate the WHO severity scale specifically in a very old population, compared with other usual prognostic tools frequently used in COVID-19, including pneumonia severity index,[7] NEWS,[4] qCSI,[5] quick SOFA (qSOFA),[8] and CURB65.[9] We included all consecutive patients aged more than 75 years and hospitalized for COVID-19 (with positive RT-PCR test). Clinical presentation

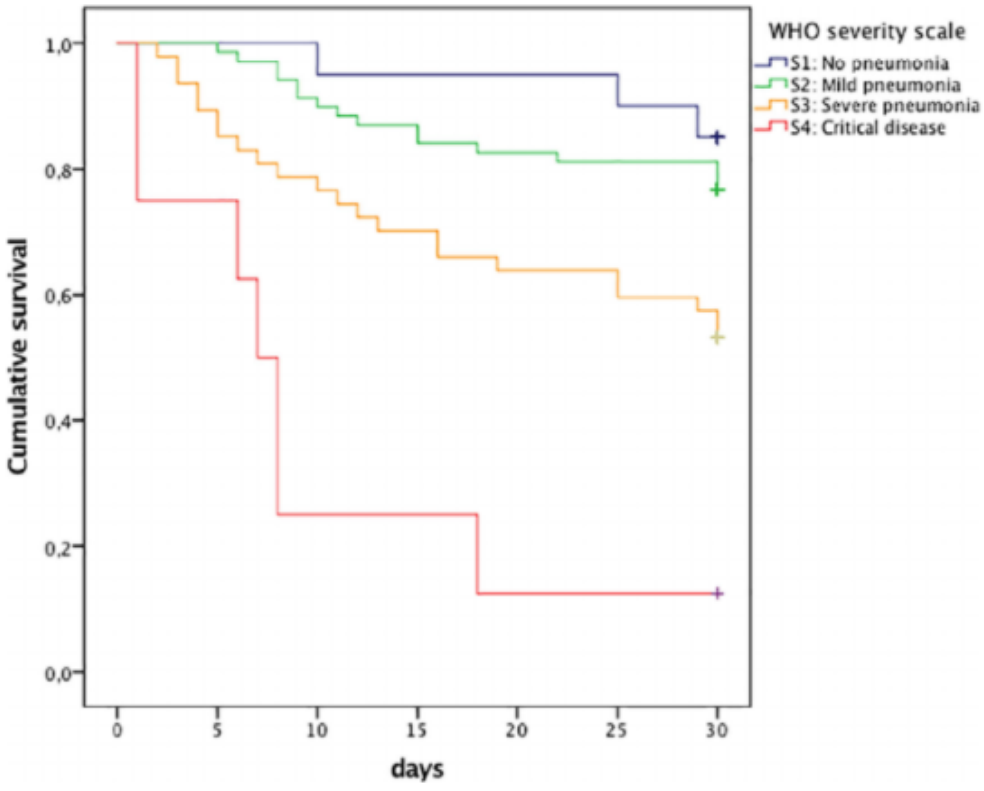

Figure 1. Short-term survival after COVID-19 according to the WHO severity scale.

See the Reply by De Matteis et al.

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and comorbidities were recorded at admission to build prognostic scores. An AUROC analysis was used to compare the ability of the various scores to predict 1-month mortality. This study was approved by the local ethics committee.

We included 142 consecutive patients (median age 86 years) who were then followed up for 1 month after admission. Overall, 48 (33.8%) patients had died by the end of follow-up. As shown in Figure 1, the WHO severity scale at admission predicted short-term mortality remarkably well. When compared with the more complex pneumonia severity index[7] (AUROC 0.74 (0.60–0.88)), the WHO severity scale (0.70 (0.60–0.79)) had similar performance when it was used to predict 1-month mortality. NEWS (0.66 (0.55–0.77)), qCSI (0.65 (0.54–0.76)), qSOFA (0.61 (0.50–0.72)), and CURB65 (0.51 (0.40–0.62)) were of lower interest in this very old comorbid population, and did not reach the performance described by Covino et al. for in-hospital mortality in younger patients.

In conclusion, these findings support the use of a simple evaluation based on respiratory function to determine prognosis after COVID-19. For this purpose, the WHO severity scale was found to have satisfactory performance in a geriatric setting. More complex evaluations that are difficult to implement at the bedside, especially in such a sanitary crisis, do not appear to add prognostic value in the short term, even in frail older patients.

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Annexe 15 : Marcello Covino, Giuseppe De Matteis, Maria Livia Burzo, Francesco Franceschi, Claudio Sandroni, ***Reply to: Comment on Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores****, Journal of the American Geriatrics Soc*

Reply to: Comment on Predicting In-Hospital Mortality in COVID-19 Older Patients with Specifically Developed Scores

To the Editor: We thank Odille et al[1] for the interest in our research and for bringing additional relevant updates to improve our work. In our manuscript, as the researchers outlined, the main finding is that the prognosis of COVID-19 older patients is mainly driven by respiratory status at admission.[2] Consequently, the severity scores including a respiratory function evaluation, such as those adopted for sepsis and pneumonia,[3-5] the general early warning scores (EWS),[6] and the specifically developed EWS, are able to stratify prognostic risk of COVID-19 patients. Likewise, as suggested by Odille et al,[1] the World Health Organization (WHO) pragmatic severity scale, which is based solely on respiratory evaluation (S1: no pneumonia; S2: pneumonia, with SpO2 ≥ 90% on room air; S3: severe pneumonia, with respiratory rate > 30 breaths/min or SpO2 < 90% on room air; S4: critical disease with acute respiratory distress syndrome),[7] could be useful for a quick patient stratification, also in emergency department setting. Nevertheless, the authors underlined that a WHO pragmatic severity scale validation in COVID-19 older patients is lacking.

Therefore, we expanded our work analyzing the performance of this index in our cohort of 210 patients aged

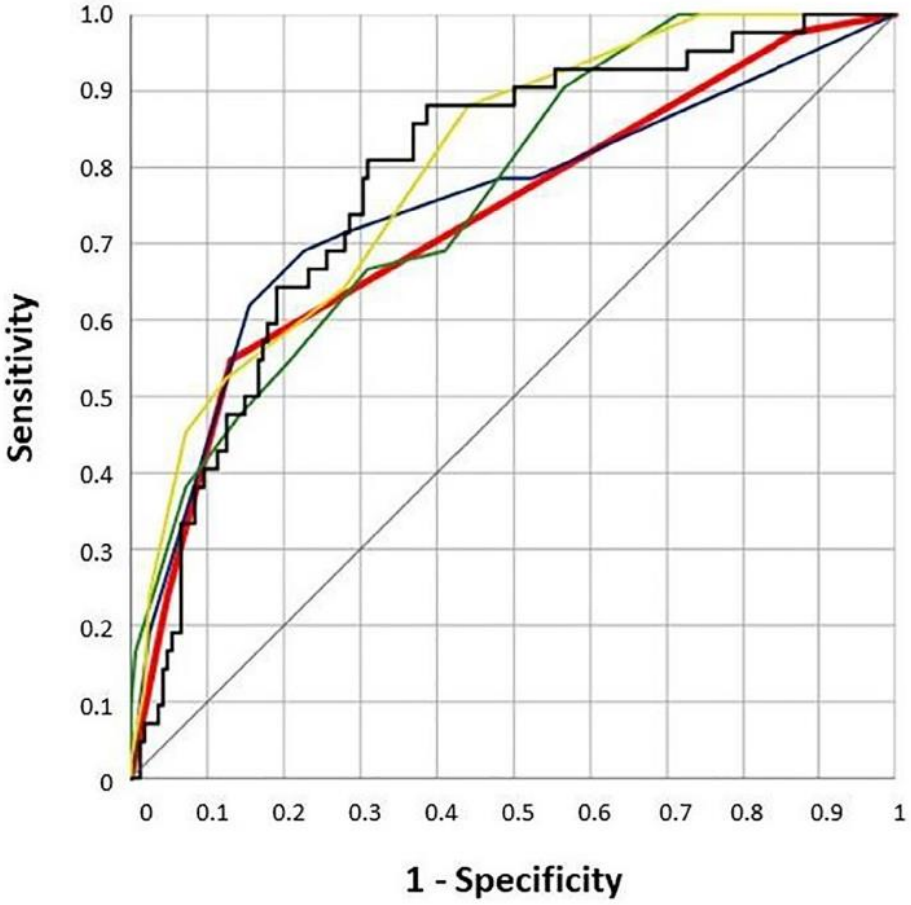

Figure 1. ROC curves of the evaluated scores with respect to in-hospital death.

This letter comments on the letter by Alain Putot

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65 years or more. Globally, among deceased patients—according to WHO severity scale—1/23 (4.3%) was in S1 group, 18/142 (12.7%) were in S2 group, 13/27 (48.1%) were in S3 group, and 10/18 (55.6%) were in S4 group. Overall, the scale had an area under receiver operating characteristic curve (AUROC) of 0.705 (0.636–0.767), with WHO score greater or equal to 2 having 47.2% (30.4–64.5) sensitivity and 89.0% (83.2–93.4) specificity for prediction of in-hospital death (Figure 1). Consequently, the WHO index showed a fairly good predictive value with respect to in-hospital death in our population, similarly to NEWS (difference between ROC areas 0.025 SE 0.038, $P = .508$), qCSI score (difference between ROC areas 0.016 SE 0.037, $P = .659$), ISARIC-4c (difference between ROC areas 0.086 SE 0.050, $P = .088$), and COVID-GRAM (difference between ROC areas 0.081 SE 0.050, $P = .106$).

To date, mainly due to age-related vulnerability and to the several complications,[8] the older patients are facing a more severe COVID-19. Therefore, the choice of an effective and quick-to-use tool could be crucial in identifying patients who could experience worse outcome. Accordingly, since all the evaluated scores had a similar performance for death risk stratification in older COVID-19 patients, we agree with Odille et al[1] that adopting the simplest index would be the best option in this population.

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CONCLUSIONS

La pandémie liée à la COVID-19 a déjà fait plus de deux millions de morts dans le monde depuis décembre 2019. Malgré les mesures de restriction mises en place et l'avènement de vaccins, le virus continue à se répandre. Les personnes âgées sont à haut risque de décès durant cette pandémie. Cependant, la majeure partie des études pronostiques sont réalisées avec des patients plus jeunes. Il paraît nécessaire de repérer précocement les formes graves afin d'améliorer la prise en charge, notamment dans la population très âgée.

Notre étude visait à déterminer au sein d'une population âgée hospitalisée pour COVID-19, la valeur pronostique des facteurs de gravités connus, la pertinence pronostique des examens complémentaires, ainsi que la fiabilité des scores pronostiques proposés.

Du 1er mars au 1er mai 2020, nous avons réalisé une étude rétrospective observationnelle portant sur des patients âgés de75 ans et plus hospitalisés pour une infection à SARS-CoV-2 dans des services de médecine aigüe de quatre centres des régions Bourgogne Franche Comté et Grand Est.

Parmi les 143 patients inclus (âge médian de 87 ans, 52% d'hommes), 48 (34%) étaient décédés à l'hôpital. Ces derniers présentaient plus fréquemment un syndrome confusionnel (P=0.01), ainsi qu'une fréquence cardiaque plus élevée à l'admission (P=0.005), tandis que la fréquence respiratoire ne différait pas entre les deux groupes (P=0.41). La présence d'une condensation alvéolaire ou d'un épanchement pleural à la tomodensitométrie était significativement associée au décès (P=0.04 ; P=0.04). Deux tiers des patients décédés présentaient une détresse respiratoire aigüe durant l'hospitalisation (contre 1% des survivants, P<0.001). Des soins palliatifs étaient entrepris pour 44% des patients décédés. A noter qu'aucun transfert en réanimation n'avait été réalisé durant cette période.

Après ajustement sur les autres facteurs pronostiques, l'âge (Hazard Ratio (intervalle de confiance 95%) (HR (IC95%)) 1.07 (1.00-1.14) ; P=0.04), le sexe masculin (HR (IC95%) 2.21 (1.00-4.88) ; P=0.048)) et les comorbidités préexistantes, appréciées par le score de Charlson (HR (IC95%)= 1.16 (1.02-1.30), étaient des facteurs de risque indépendants de mortalité.

Parmi les variables biologiques usuelles, les biomarqueurs cardiaques à l'admission (*N terminal Pro Brain Natriuretic Peptide,* troponine Ic) ainsi que l'albuminémie étaient celles qui présentaient les meilleures performances pronostiques.

Le score *Pneumonia Severity Index* (PSI) était le score pronostique qui présentait les meilleures performances (*area under the receiver operating characteristic* (AUROC) (IC95%) 0.74 (0.60-0.88)), suivi par le score spécifique à la COVID-19 proposé par l'OMS (AUROC (IC95%) 0.70 (0.60-0.79)). Toutefois, devant la complexité du score PSI, le score OMS, facile d'utilisation, apparait en population gériatrique comme un outil de choix pour apprécier le pronostic à court terme.

Cette étude permet de mieux cibler les personnes très âgées à risque d'évolution défavorable lors d'une infection à SARS-CoV-2. La création d'un score pronostique spécifique aux patients âgés permettrait d'optimiser les parcours de soins, objectif plus que jamais nécessaire dans le contexte actuel exceptionnel de ressources limitées.

Le Président du jury,

Pr. P. MANCKOUNDIA

Vu et permis d'imprimer
Dijon, le 10 MARS 2020
Le Doyen

Pr. M. MAYNADIÉ

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TITRE DE LA THESE : FACTEURS PRONOSTIQUES DE LA COVID-19 CHEZ LES PATIENTS DE PLUS DE 75 ANS : ETUDE OBSERVATIONNELLE MULTICENTRIQUE

AUTEUR : ODILLE GEOFFREY

RESUME :

Introduction : Les personnes âgées sont à haut risque de décès durant la pandémie à COVID-19. Pourtant, la majeure partie des études pronostiques sont réalisées chez des patients plus jeunes. Notre étude visait à déterminer la valeur pronostique des facteurs de gravité connus et la fiabilité des scores pronostiques validés pour les pneumonies bactériennes, spécifiquement dans une population très âgée, hospitalisée pour une infection à SARS-CoV-2.

Matériel et méthodes : Il s'agit d'une étude observationnelle, rétrospective, conduite dans 4 centres hospitaliers des régions Bourgogne-Franche Comté et Grand Est, du 1/3 au 1//5/2020. Tous les patients âgés de plus de 75 ans hospitalisés pour COVID-19 dans des services de médecine aigue d'un de ces centres étaient éligibles. Les facteurs associés à la mortalité à 1 mois étaient étudiés en analyses uni et multivariée en utilisant un modèle de Cox. Les scores et biomarqueurs étaient comparés selon leurs performances respectives (*area under the receiver operating characteristic*, AUROC)

Résultats : Parmi les 143 patients consécutifs hospitalisés pour COVID-19 et inclus dans l'étude (âge médian 87 ans, 52% d'hommes), 48 (34%) étaient décédés à 1 mois. Comparés aux survivants, les patients décédés présentaient plus fréquemment un syndrome confusionnel et une tachycardie à l'admission (P=0.01 ; P=0.005) Toutefois, la fréquence respiratoire ne différait pas entre les deux groupes (P=0.41). La présence d'une condensation alvéolaire ou d'un épanchement pleural au scanner était significativement associée au décès (P=0.04 ; P=0.04). Deux tiers des patients décédés présentaient une détresse respiratoire aigüe durant l'hospitalisation (vs. 1% des survivants, $P < 0.001$). Des soins palliatifs étaient entrepris pour 44% des patients décédés. L'analyse multivariée que l'âge (Hazard Ratio (Intervalle de Confiance à 95 %) (HR (IC95%) : 1.07 (1.00-1.14) par année, P = 0.04), le sexe masculin (HR (IC95%) : 2.21 (1.00-4.88) ; P = 0.048)) et les comorbidités appréciées par le score de Charlson (HR (IC95%) : 1.16 (1.02-1.30) par point ; P = 0.021)) étaient les facteurs associés à la mortalité intra-hospitalière. Les biomarqueurs sériques présentant les meilleurs valeurs pronostiques à l'admission étaient le *N terminal Pro Brain Natriuretic Peptide (AUROC* (IC95%) : 0.71 (0.60-0.82), la troponine Ic *(AUROC* (IC95%) : 0.70 (0.55-0.85) et l'albuminémie (*AUROC* (IC95%) : 0.69 (0.57-0.84). Parmi les scores pronostiques, le score de Fine présentait les meilleures performances (AUROC (IC95%) : 0.74 (0.60-0.88)) suivi par le score de l'OMS (AUROC (IC95%) : 0.70 [0.60-0.79]).

Conclusion : L'âge, le sexe masculin et un taux élevé de comorbidités étaient retrouvés dans notre étude comme facteurs de risque indépendant de décès chez le sujet âgé hospitalisé pour COVID-19. Le score OMS, basé exclusivement sur l'appréciation de la fonction respiratoire, semble être un outil pronostique de choix pour l'évolution initiale.

MOTS-CLES: COVID-19, SARS-COV-2, POPULATION AGEE, MORTALITE, PRONOSTIC, COMORBIDITES