Timing and Causes of Death in Severe COVID-19 Patients

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Abstract

Introduction: Although early identified as a deadly infectious disease, the precise mortality rate of the most severe forms of COVID-19 is a matter of debate. To the best of our knowledge, no study investigated so far, the causes that ultimately led to death as well as the relation between timing and causes of death.

Material & Methods: We performed a retrospective study in eight ICU within eight French hospitals. All consecutive adult patients (aged≥ 18 years old) admitted in the ICU with a PCR-confirmed SARS-CoV-2 infection and acute respiratory failure were included in the analysis. Causes and timing of death were reported based on medical records. A binomial logistic regression statistical analysis was performed to identify the determinants associated with ICU-mortality.

Results: From March 1st, 2020 to April 28th, 287 patients were admitted to ICU for SARS-CoV-2 related acute respiratory failure. COVID-19 related multiple organ dysfunction syndromes (MODS) was the leading cause of death (29%, n=27/93). End-of-life decisions occurred in 25% of patients (n=23/93). Secondary infections-related MODS accounted for 21% of ICU death, with a majority of ventilator-associated pneumonia. Fatal ischemic events (venous or arterial) occurred in 12% of patients. Refractory hypoxemia was a relatively uncommon cause of death and occurred only in 8 cases (9%). Regarding the timing of death, only one death occurred during the first three days of ICU admission. Determinants associated with ICU-mortality in logistic regression were age >65, requirement for vasopressors, renal replacement therapy and extracorporeal membrane oxygenation.

Conclusion: Our data suggest the existence of a specific pattern of outcome in severe COVID-19 patients compared to severe bacterial and viral pneumonia, consisting in a high proportion of delayed COVID-19 related MODS.

Introduction

The precise mortality rate of the most severe forms of SARS-CoV-2 infections that are admitted in the intensive care unit (ICU) vary among studies, ranging from 8.1–30%[1–3]. Such discrepancy could rely on the heterogeneity of several factors such as heterogeneity of admission criteria, patient's characteristics at admission or differences in management. Therefore, analysis of global mortality as a primary outcome seems even more difficult to interpret.

In this context, a better characterization of both timing and causes of death in severe COVID-19 patients seems mandatory to better understand the disease and guide further researches given that therapeutic approaches depend on the phenotypic presentation. Indeed, such discrepancy in patients' characteristics and phenotype[4] as well as the cause of death, might explain the recent failure of the majority of interventional studies in COVID-19 despite a plausible scientific rational[5,6].

We herein report the multicentre retrospective analysis of 287 consecutive severe COVID-19 patients admitted in eight French ICUs with the aim to determine the timing and the causes of death.

Material And Methods

Study design and participants

We performed a retrospective study in eight ICU within seven French hospitals (Gustave Roussy, Villejuif; Cochin Hospital, Paris; Hotel Dieu Hospital, Nantes; Jean Minjoz Hospital, Besançon; Centre Hospitalier Intercommunal, Alençon; Centre Hospitalier Mémorial, Saint-Lô and Lariboisière Hospital, Paris). The study gathered consecutive adult patients (aged ≥ 18 years old) admitted in the ICU with a PCR-confirmed SARS-CoV-2 infection and acute respiratory failure. Demographic, clinical, laboratory, treatment, and outcome data were collected from electronic medical records using a standardized data collection form. An independent physician (CdR) checked all data. The Research Ethics Commission of the Gustave Roussy Institute approved the study. The study was registered at the French National Commission on Informatics and Liberty and the French National Institute for Health Data.

Definitions

Laboratory confirmation of COVID-19 was based upon SARS-CoV-2 detection by real-time RT-PCR from nasal swabs or lower respiratory tract secretions. Simplified Acute Physiology Score 2 and the Sequential Organ Failure Assessment (SOFA) scores assessed infection severity at admission. Patients were considered immunocompromised if one or more of the following conditions were observed: patients with solid tumours treated with chemotherapy in the last 3 months or progressive metastatic disease, hematologic malignancies, solid organ transplantation, HIV infection with or without AIDS, treatment with corticosteroids (> 3 months at any dosage or ≥ 1 mg/kg prednisone equivalent per day for > 7 days), or treatment with other immunosuppressive drugs. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin definition. Obesity was defined as a body mass index superior to 30 kg/m^2.

Analysis and characteristics of death in COVID-19 patients

One senior intensivist was responsible for determining and reporting the cause of death using medical records for each centre. COVID-19 related Multiple Organ Dysfunction Syndrom (MODS) was defined as the dysfunction of two or more organs, including pulmonary, coagulation, cardiac, neurological, renal, hepatic, and gastrointestinal manifestations that were not pre-existent to SARS-CoV-2 infection[7]. ICU-acquired infections were defined as any new onset of probable or definite infection that developed after 48 h from ICU admission. ICU-acquired pneumonia definition was based upon French guidelines[8]. Of note, we also considered secondary infections-related MODS as a cause of death. Refractory hypoxaemia was defined as a PaO_2 below 60 mmHg for more than one hour while receiving a FiO_2 1.0 [9].

Management

Patients were managed according to local standards of care in each centre in the pandemic context of the SARS-CoV-2 outbreak. Patients developing ARDS received neuromuscular blockade, high PEEP levels, and prone positioning according to international guidelines[10]. Extracorporeal Membrane Oxygenation (ECMO) was used as salvage therapy in cases of persistent refractory hypoxaemia depending on centre expertise

and availability. In each centre, end-of-life decisions to withhold or withdraw life support were taken on collectively when all participants considered maintenance or increase in life-sustaining therapies as futile because death would irremediably occur in a short-term manner.

Statistics

For the descriptive analysis, continuous variables were expressed as median (interquartile range) and categorical variables as numbers (percentages). Comparisons were performed relying on the Fisher exact test or $\chi 2$ test for categorical data and the Kruskal-Wallis or Wilcoxon test for continuous data. Time for admission to ICU death was classified according to causes of death and compared using a one-way ANOVA with Dunn's multiple comparison test. To identify independent predictors of hospital mortality, characteristics associated with P values less than .1 by univariate analysis or deemed clinically relevant were included in a multivariable logistic regression model with backward selection. Non-log-linear continuous variables were dichotomized. All analyses were performed using R version 3.6 (R project, Vienna).

Results

Patients' characteristics

From March 1^{st,} 2020 to April 28th, 287 patients were admitted to the eight identified ICUs for SARS-CoV-2 related acute respiratory failure. Their main characteristics are summarized in Table 1. Patients were mostly male (n = 144, 82%), with a median age of 63 (55–73) years. Arterial hypertension and obesity were the prominent comorbid conditions. Most of them were mechanically ventilated (91%) with a median duration of 19 days [25th – 75th IQR: 13–28 days] and approximately two-thirds underwent prone positioning. Rescue extracorporeal membrane oxygenation (ECMO) was used in 25 (8%) patients.

Table 1
Characteristics of the patients

	All patients (n = 287)	Survivors (n = 194)	Deceased in ICU (n = 93)	p
Age, years	63 [54–71]	61.00 [52–69]	68.00 [61–75]	< 0.01
Female gender	55 (19.2)	40 (20.6)	15 (16.1)	0.46
Body mass index	28 [25–32]	28 [25–32]	28 [25–31]	0.94
Comorbid conditions				
Obesity	168 (61.3)	116 (62.7)	52 (58.4)	0.58
Arterial hypertension	137 (47.7)	89 (45.9)	48 (51.6)	0.43
Diabetes mellitus	84 (29.3)	54 (27.8)	30 (32.3)	0.53
Tobacco use	38 (13.2)	26 (13.4)	12 (12.9)	1
COPD	34 (11.8)	22 (11.3)	12 (12.9)	0.85
Chronic kidney disease	22 (7.7)	11 (5.7)	11 (11.8)	0.11
Cirrhosis	2 (0.7)	1 (0.5)	1 (1.1)	1
Characteristics on ICU admission				
SAPS2, points	59 [29–53]	36 [28–46]	47 [38–63]	< 0.01
SOFA, points	6 [4–9]	5 [3–8]	8 [5–10]	< 0.01
Initial P/F ratio	103 [76–150]	113 [80–150]	86 [70–124]	< 0.01
Interval from symptom onset to ICU admission	7 [4–10]	7 [4–10]	7 [4–10]	0.93
ICU management				
Mechanical ventilation	258 (91.5)	166 (87.8)	92 (98.9)	< 0.01
Norepinephrine	217 (75.9)	130 (67.4)	87 (93.5)	< 0.01
Neuromuscular blockade	244 (85.0)	154 (79.4)	90 (96.8)	< 0.01

ICU: Intensive Care Unit; COPD: Chronique obstructive pulmonary Disease; SAPS: simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment

	All patients (n = 287)	Survivors (n = 194)	Deceased in ICU (n = 93)	p
Prone positioning	**194 (67,6)**	**113 (58.2)**	**81 (87.1)**	< 0.01
Extracorporeal membrane oxygenation	**25 (8,7)**	**11 (6.4)**	**14 (15.7)**	0.03
Renal replacement therapy	**82 (28.6)**	**38 (19.6)**	**44 (47.3)**	< 0.01
Specific treatment				
Hydroxychloroquine	**84 (29.3)**	**55 (28.5)**	**29 (31.5)**	0.70
Azithromycin	**75 (26.1)**	**48 (24.9)**	**27 (29.3)**	0.51
Lopinavir/ritonavir	**61 (21.3)**	**33 (17.1)**	**28 (30.4)**	0.02
Corticosteroids	**55 (19.2)**	**31 (18.0)**	**24 (27.3)**	0.12
Remdesivir	**10 (3.4)**	**9 (4.7)**	**1 (1.1)**	0.23
Tocilizumab	**8 (2.8)**	**3 (1.6)**	**5 (5.4)**	0.14
Outcomes				
Length of stay, days	**18.00 [10–30]**	**19.00 [12–31]**	**15 [7–27]**	0.04
Duration of mechanical ventilation, days	**19 [13–28]**	**17.00 [11–28]**	**25.00 [14–28]**	0.15
Secondary infection	**151 (53.0)**	**97 (50.3)**	**54 (58.7)**	0.23

ICU: Intensive Care Unit; COPD: Chronique obstructive pulmonary Disease; SAPS: simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment

Risk factors for ICU-death

The overall ICU-mortality rate was 32.4% (n = 93). In univariate analysis, deceased patients in ICU were older ($p < 0.001$), with higher SOFA and SAPS II scores ($p < 0.001$ for both) and a higher rate of organ support (Table 1). In multivariate analysis, age > 65, requirement for vasopressors, RRT and ECMO were independently associated with an increased mortality (Fig. 2).

Timing and causes of death

COVID-19-related MODS was the leading cause of death (29%, n = 27/93), with a median time from ICU admission to death of 14 days [25th – 75th IQR: 7–19 days] (Table 2). ICU death resulted from end-of-life decisions in 25% of patients (n = 23/93). Secondary infections-related MODS accounted for 21% of ICU death, with a majority of ICU-acquired pneumonia (ICU-AP). Fatal ischemic events were responsible for ICU death in 12.9% of patients (with 7 cases of pulmonary embolism, 2 strokes, 2 mesenteric ischemia, and 1

myocardial infarction). Refractory hypoxaemia was a relatively uncommon cause of death among COVID-19 patients and occurred in 8 cases (9%).

Table 2
Baseline Characteristics and Outcome of Covid-19 patients who died in ICU stratified according to cause of death

	COVID related MODS (n = 27)	End of Life Decision (n = 23)	Secondary Infection-related MODS (n = 20)	Fatal Ischemic Event (n = 12)	Refractory Hypoxemia (n = 8)	Others* (n = 3)	p
Age, years	71 [65–77]	74 [69–77]	64 [60–69]	60 [56–63]	67 [58–70]	62 [61–65]	< 0.01
Female gender	4 (14.8)	2 (8.7)	3 (15.0)	4 (33.3)	2 (25.0)	0 (0)	0.46
Body mass index	29 [26–32]	27 [25–29]	28 [26–30]	29 [28–32]	28 [24–31]	26 [25–29]	0.54
Comorbid conditions							
Obesity	17 (63)	11 (52.4)	10 (50)	8 (66.7)	4 (66.7)	2 (66.7)	0.89
Arterial hypertension	15 (55.6)	9 (39.1)	11 (55)	7 (58.3)	5 (62.5)	1 (33.3)	0.75
Diabetes mellitus	8 (29.6)	9 (39.1)	6 (30)	5 (41.7)	2 (25)	0 (0)	0.74
Tobacco use	6 (22.2)	2 (8.7)	2 (10)	1 (8.3)	1 (12.5)	0 (0)	0.66
COPD	3 (11.1)	4 (17.4)	3 (15)	1 (8.3)	1 (12.5)	0 (0)	0.94
Chronic kidney disease	4 (14.8)	2 (8.7)	3 (15)	1 (8.3)	1 (12.5)	0 (0)	0.95
Cirrhosis	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)	0.69
Characteristics on ICU admission							
SAPS2, points	47 [35–62]	50 [39–62]	47 [44–64]	42 [27–52]	47 [34–62]	47 [40–65]	0.77
SOFA, points	8 [5–9]	8 [5–10]	8 [6–11]	9 [8–11]	8 [7–9]	9 [7–9]	0.89

*one patient died from iatrogenic event, one patient died from cardiac arrest of unknown origin and one patient died from invasive aspergillosis. ICU: Intensive Care Unit; COPD: Chronique obstructive pulmonary Disease; SAPS: simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment

	COVID related MODS (n = 27)	End of Life Decision (n = 23)	Secondary Infection-related MODS (n = 20)	Fatal Ischemic Event (n = 12)	Refractory Hypoxemia (n = 8)	Others* (n = 3)	p
Initial P/F ratio	99 [70–134]	100 [82–167]	80 [71–81]	98 [60–191]	90 [56–121]	70 [65–130]	0.26
Interval from symptom onset to ICU admission	7 [6–10]	8 [4–10]	7 [5–10]	10 [7–10]	8 [6–9]	8 [6–9]	0.91
ICU management							
Mechanical ventilation	27 (100)	23 (100)	19 (95)	12 (100)	8 (100)	3 (100)	0.60
Norepinephrine	27 (100)	21 (91.3)	19 (95)	11 (91.7)	6 (75)	3 (100)	0.22
Neuromuscular blockade	27 (100)	20 (87)	20 (100)	12 (100)	8 (100)	3 (100)	0.09
Prone positioning	24 (88.9)	17 (73.9)	19 (95)	10 (83.3)	8 (100)	3 (100)	0.26
Extracorporeal membrane oxygenation	2 (7.7)	2 (8.7)	5 (27.8)	3 (27.3)	0 (0.0)	2 (66.7)	0.03
Renal replacement therapy	4 (14.8)	2 (8.7)	3 (15)	1 (8.3)	1 (12.5)	0 (0)	0.95
Specific treatment							
Hydroxychloroquine	10 (37)	5 (21.7)	8 (40)	2 (16.7)	3 (100)	1 (14.3)	0.06
Azithomycin	8 (29.6)	5 (21.7)	9 (45)	2 (16.7)	2 (66.7)	1 (14.3)	0.24
Lopinavir/ritonavir	11 (40.7)	6 (26.1)	6 (30)	3 (25)	1 (33.3)	1 (14.3)	0.76
Corticosteroids	9 (34.6)	4 (17.4)	6 (33.3)	3 (27.3)	1 (33.3)	1 (14.3)	0.73
Tocilizumab	3 (11.1)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	0.87
Remdesivir	0 (0)	0 (0)	1 (5.0)	0 (0)	0 (0)	0 (0)	0.60

*one patient died from iatrogenic event, one patient died from cardiac arrest of unknown origin and one patient died from invasive aspergillosis. ICU: Intensive Care Unit; COPD: Chronique obstructive pulmonary Disease; SAPS: simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment

	COVID related MODS (n = 27)	End of Life Decision (n = 23)	Secondary Infection-related MODS (n = 20)	Fatal Ischemic Event (n = 12)	Refractory Hypoxemia (n = 8)	Others* (n = 3)	p
Outcomes							
Length of stay, days	**14** [7–19]	**16 [9–27]**	**25 [12–30]**	**16 [6–27]**	**12 [9–27]**	**32 [19–40]**	0.41
Duration of mechanical ventilation, days	**15 [11–23]**	**25 [9–28]**	**28 [28–28]**	**28 [22–28]**	**32 [30–40]**	**28 [9–28]**	<0.01

*one patient died from iatrogenic event, one patient died from cardiac arrest of unknown origin and one patient died from invasive aspergillosis. ICU: Intensive Care Unit; COPD: Chronique obstructive pulmonary Disease; SAPS: simplified acute physiology score; SOFA: Sepsis-related Organ Failure Assessment

Regarding the timing of death, only one patient died during the first three days after ICU admission. The median time from ICU admission to death was 15 days [25th – 75th IQR: 7–27 days]. We found no statistical differences in time from admission to ICU death between the different causes of death. The distribution of death according to time from admission is depicted in Fig. 1.

Discussion

To the best of our knowledge, this is the first study reporting causes and timing of death in severe COVID-19 patients. COVID-19-related MODS and end-of-life decision were the two main causes of death in severe COVID-19 patients admitted in ICU. Regarding the timing of death, only one patient died within three days.

Although understanding causes of mortality is of major interest, identifying the precise pathway to death faces several constraints. First, determining the precise cause of death is highly dependent on the implemented strategies of diagnosis that may vary among centres and countries. Second, several diseases may be deeply intertwined and lead to death, especially after a protracted period of ICU stay that is associated with the occurrence of ICU-acquired complications. Thus, the attributable mortality of each potential causes of death remains highly debated, especially in severe COVID-19 patients[11]. Autopsy findings and histopathological post-mortem evidences are therefore crucial to improve our understanding of severe COVID-19, especially in distinguishing the exact cause of death from other contributing factors. A recent review focusing on post-mortem examinations in COVID-19 patients reported pulmonary embolism as a major cause of death among COVID-19 patients, with a high prevalence of peripheral deep venous thrombo-embolism [12]. These observations are in line with several studies reporting a high proportion of both venous and arterial thrombotic events in severe COVID-19 patients[13–15]. Consequently, one can hypothesize that the high incidence of COVID-19 related MODS we observed might rely on diffuse

thromboembolic complications. In this perspective, the 13% rate of fatal ischemic events we report might be underestimated.

Unlike what is observed in severe COVID-19 patients in this study, the early mortality is high in severe bacterial or viral pneumonia. In septic shock, approximately one third of patients die during the first 72 hours, with a vast majority of primary infection related MODS[16]. Early mortality is also high in severe viral pneumonia, with the identification of bacterial co-infection as a major cause of death[17]. This early mortality has been ascribed to the existence of an overwhelming inflammation at initial stages of septic shock, including the overexpression of pro-inflammatory cytokines such as IL-6, IL-12 and TNFα[18]. In line with our results, a recent study reported IL-6 serum levels to be 27-times lower in COVID-19 patients when compared to septic shock patients, therefore questioning the existence of a cytokine storm in COVID-19[19]. Once again, the in-hospital course of COVID-19 patients admitted in ICU is different, with a low reported rate of bacterial co-infection[20].

Apart from COVID-19 related MODS, end of life decision accounted for 25% of death among severe COVID-19 patients. Ethical issues in the ICU have been a challenging discussion in the COVID-19 pandemic context for two main reasons that are 1/ the higher mortality rate in the elderly and frail patients and 2/ the shortage of medical resources. Therefore, the high rate of life-sustaining therapies discontinuation could reflect the existence of unusual external constraints. However, two points argues against this assertion. First, such a proportion has been previously reported, with end-of-life decision as the main cause of death in septic shock patients[16]. Second, the median time from admission to death in patients with life sustaining therapies discontinuation is 16 days, suggesting withdrawal of care has been decided in a non-emergency context.

This study acknowledges two main limitations. First, such a retrospective study limits the establishment of a definite causality inference. Second, the multicentre design is associated with differences in diagnosis procedures and the determination of causes of death was left at the discretion of the physician in charge.

Conclusion

We have identified COVID-19 related MODS and end-of-life decision as the two leading causes of death in severe COVID-19 patients admitted in the ICU, with a vast majority of them occurring two weeks after admission. These results urge to continue attempts to better understand the pathophysiology of this disease and to develop uniform diagnosis strategies.

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Figures

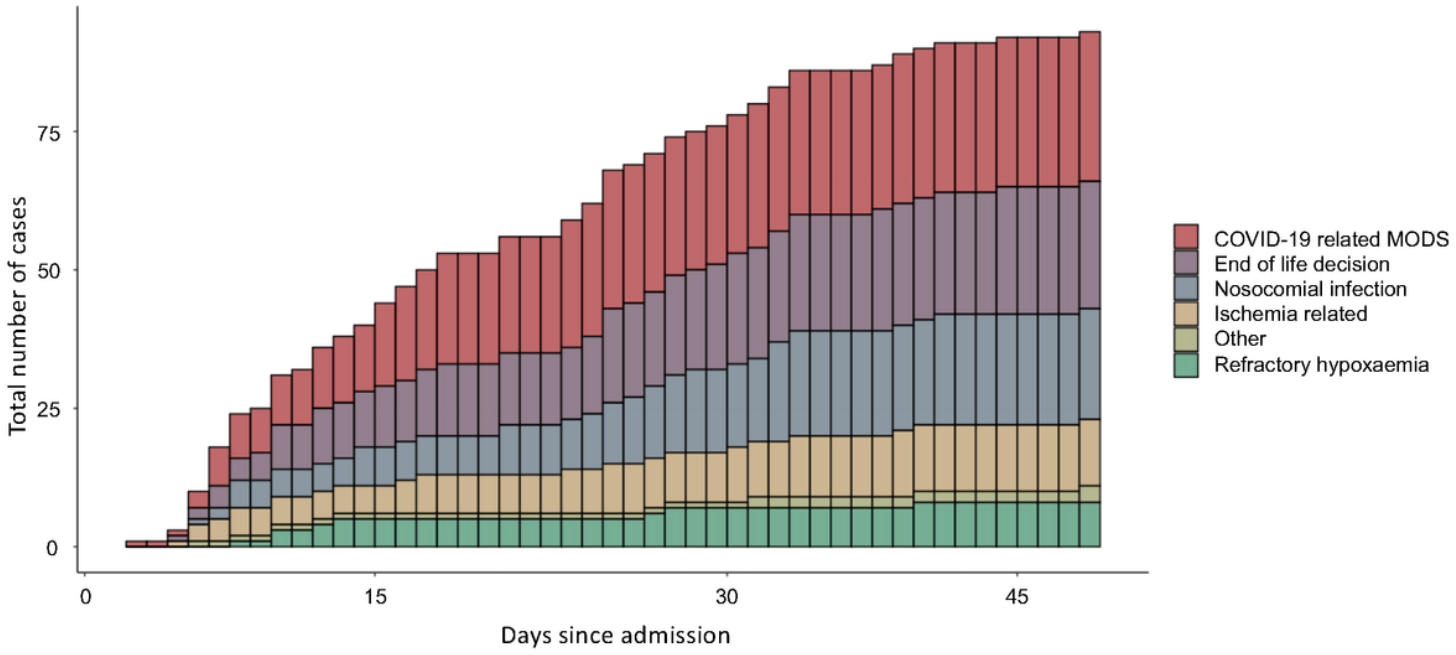

Figure 1

Cumulative incidence of ICU-mortality during hospitalization. ICU: Intensive Care Unit, MODS: Multiple Organ Dysfunction Syndrome

parameters		Odds ratio		p
Age	< 65		Reference	
	> 65		3.58 (1.86, 7.10)	<0.01
Chronic kidney disease			1.63 (0.51, 5.46)	0.41
P/F at admission	> 100		Reference	
	< 100		1.39 (0.70, 2.75)	0.34
Mechanical ventilation			2.27 (0.19, 58.10)	0.55
Prone positioning			2.33 (0.96, 6.03)	0.07
Neuromuscular blockers			2.00 (0.49, 10.50)	0.36
Norepinephrine			3.79 (1.45, 11.53)	0.01
Renal replacement therapy			2.54 (1.30, 5.02)	<0.01
Extracorporeal membrane oxygenation			3.23 (1.18, 9.30)	0.03

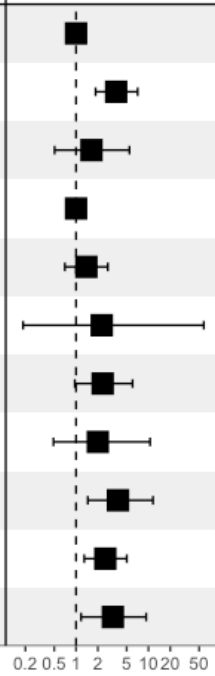

Figure 2

Forrest plot of factors associated with ICU-mortality, binary logistic regression