Upper Gastrointestinal Tract Bleeding as a Predictor of Mortality in COVID-19 Patients Admitted to RSUP Dr. Sardjito, Yogyakarta, Indonesia

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Abstract. This retrospective cohort study explored the association between Upper Gastrointestinal Tract Bleeding (UGIB) and mortality in adult COVID-19 patients admitted to RSUP Dr. Sardjito Yogyakarta hospital from January 2021 to October 2022. Data, sourced from electronic medical records (EMRs) and analyzed using R Studio, aimed to discern if UGIB could predict mortality in COVID-19 patients, considering other relevant comorbidities. The univariate analysis identified several significant mortality-associated factors. Notably, UGIB presented an odds ratio (OR) of 2.14 (95% CI 1.48-3.11, $p < 0.001$) for increased mortality. Type 2 diabetes mellitus (OR 1.56, 95% CI 1.34-1.81), hypoalbuminemia (OR 2.05, 95% CI 1.70-2.48), hyperkalemia (OR 3.35, 95% CI 2.44-4.67), and renal impairment (OR 2.91, 95% CI 2.41-3.53) also exhibited significant associations. In contrast, being female reduced mortality risk (OR 0.78, 95% CI 0.69-0.90). The multivariate analysis, after adjusting for influential factors, indicated UGIB as an independent predictor with an OR of 1.68 (95% CI 1.02-2.79, $p = 0.042$). The results underscore UGIB's significance in predicting COVID-19 patient mortality, suggesting the need for proactive interventions to enhance patient management and outcomes.
Keywords: Upper gastrointestinal bleeding, COVID-19, mortality, claim-based registry, electronic medical records

1 Introduction

Cases of viral pneumonia associated with a severe acute respiratory syndrome were first reported in December 2019 in the city of Wuhan, China. Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the causative agent of coronavirus disease 2019 (COVID-19), was identified in January 2020. The primary symptoms of COVID-19 include fever, dry cough, dyspnea, fatigue, myalgia, and headache. [1]

Similar to other coronaviruses, SARS-CoV-2 infects the gastrointestinal tract. Several case reports have described the occurrence of gastrointestinal bleeding in COVID-19 patients despite common gastrointestinal symptoms such as diarrhea, nausea, and vomiting. [2]

The use of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), steroids, antiviral agents and anticoagulation in COVID-19 infection are also known to increase the risk of gastrointestinal bleeding significantly. [3]

Previous study said that individuals with COVID-19 were found to be at risk for gastrointestinal bleeding, especially upper gastrointestinal bleeding (UGIB). [2]

Another study said that UGIB was suspected in 62.5% of the COVID-19 patients and lower GI bleeding (LGIB) in 37.5% COVID-19 patients. There was also no statistically significant difference in ICU admission and mortality with the use of anticoagulation in COVID-19 patients. [4]

Meanwhile, previous systematic review and meta-analysis that aggregate data from 10 studies showed an overall gastrointestinal bleeding rate of 2%, of which 1% for UGIB and 1% for LGIB, respectively. [3]

A high prevalence of peptic ulcer disease complicated by bleeding was noticed in patients with moderate-to-severe acute respiratory distress syndrome caused by COVID-19. [2]

Previous study said that gastrointestinal bleeding was not the independent predictor of mortality in COVID-19 patients. Higher mortality in COVID-19 patients is likely secondary to respiratory failure and critical illness as seen in prior studies and may not be directly secondary to gastrointestinal bleeding. [2]

However, the real burden of gastrointestinal bleeding in COVID-19 patients still needs to be clarified. This study is conducted to know whether upper gastrointestinal tract bleeding can be a predictor of mortality in COVID-19 patients.

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2 Materials and Methods

2.1 Study Design and Setting

This study employed a retrospective cohort design. It utilized data extracted from the claim-based registry of electronic medical records (EMRs) at the RSUP Dr. Sardjito Yogyakarta, a tertiary referral hospital. The data utilized for the study spanned from January 2021 to October 2022.

2.2 Study Population and Sampling Method

The study cohort included all adult patients with a confirmed diagnosis of COVID-19 admitted to the hospital during the study period. The research utilized a total sampling method due to the retrospective nature of the study. This approach permitted the inclusion of all patients meeting the defined eligibility criteria within the specified timeframe.

2.3 Data Collection

Data was systematically extracted from the hospital's claim-based registry. The collected variables encompassed demographic factors (age, sex), comorbidities (as determined by ICD-10 codes, focusing on the top 10 comorbidities occurring in COVID-19 patients, as well as other relevant comorbidities deemed significant as potential predictors), the occurrence of UGIB, the level of care provided (intensive or non-intensive), and patient outcomes (including mortality status and length of stay). To ensure data integrity and efficient management, the Research Electronic Data Capture (REDCap) platform was employed. This secure and user-friendly application facilitated both effective data handling and subsequent analysis.

2.4 Statistical Analysis

Statistical analyses were performed using R Studio, specifically employing the 'tidyverse' and 'gtsummary' packages. The 'tidyverse' package was utilized for data cleaning and pre-processing, while 'gtsummary' was leveraged for generating analytical tables. Depending on data normality, assessed through the Shapiro-Wilk test, continuous data was presented as either a median with an interquartile range (IQR) or a mean with a standard deviation (SD). Independent t-tests, Wilcoxon tests, and Chi-square tests were used to evaluate differences in means, medians, and percentages, respectively. A multivariate logistic regression model was created for variable selection based on domain knowledge and a stepwise analysis method considering the p-value and the highest Akaike information criterion (AIC) index. The results of both univariate and multivariate analyses were displayed concurrently for comparative purposes.

2.5 Ethical Considerations

The research design adhered to the principles of the Declaration of Helsinki and Good Clinical Practice. As the study involved a retrospective analysis of existing data, the risk to patients was minimal. All patient information was anonymized before the analysis stage to ensure the protection of patient privacy. The study protocol was submitted for approval to the Institutional Review Board or Ethics Committee before initiating the research.

3 Results

Figure 1 presents the top ten comorbidities in a cohort of 3647 COVID-19 patients at the RSUP Dr. Sardjito Yogyakarta hospital. This large and diverse patient pool allowed for a comprehensive examination of the comorbidities associated with COVID-19.

The most prevalent comorbidity was type 2 diabetes mellitus (T2DM) without complications, followed by essential (primary) hypertension (HT). The third most common comorbidity was disorders of plasma-protein metabolism, such as hypoalbuminemia, and acute kidney failure, ranked fourth. The fifth most common comorbidity was hyponatremia. Nonspecific elevated levels of transaminase and lactic acid dehydrogenase took the sixth spot, with unspecified anemia ranking seventh. Hypokalemia was the eighth most common comorbidity, with urinary tract infection (UTI), site not specified, coming in ninth, and hyperkalemia rounding out the top ten.

In addition to these, upper GIT bleeding also emerged as a significant medical event within this cohort. There were 127 cases of UGIB in 3647 COVID-19 patients. The rest, 3520 cases did not experience UGIB.

These identified comorbidities, along with upper GIT bleeding, were subsequently employed as potential predictors in our study. The hypothesis was that the presence of these comorbidities might significantly influence patient outcomes, particularly mortality, within our COVID-19 patient cohort.

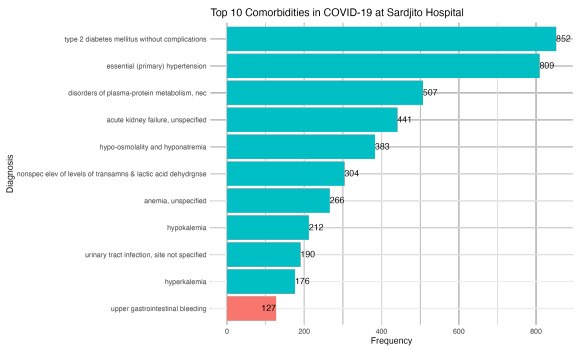

Fig. 1. Top ten comorbidities in a cohort of 3647 COVID-19 patients at the RSUP Dr. Sardjito Yogyakarta hospital, along with the incidence of upper GIT bleeding.

Table 1 provides a comprehensive overview of the demographic and clinical characteristics of the 3647 COVID-19 patient in this study, alongside the distribution of the primary predictors, which encompass various comorbidities and the occurrence of upper GIT bleeding.

In terms of demographic characteristics, the median age of patients was 55 years old, with an interquartile range (IQR) from 42 to 64 years old, signifying that the patient population was primarily middle-aged to elderly. The sex distribution was almost equal, with males representing 49.8% of the cohort.

The median length of stay (LOS) in the hospital was six days, ranging between three to ten days. The majority of patients (90.4%) were treated in non-intensive care units.

As for the presence of comorbidities, type 2 diabetes mellitus without complication was the most prevalent, affecting 23% of the patients, closely followed by hypertension. Hypoalbuminemia, renal impairment, elevated transaminase levels, hyponatremia and anemia affected 7.3-14% of the patients. Meanwhile hypokalemia, urinary tract infection, and hyperkalemia were observed in 4.8-5.8% of COVID-19 patients. Upper GIT bleeding was present in 3.5% of cases. The prevalence of cardiovascular conditions was also of interest. Stroke, coronary arterial disease (CAD), arrhythmia and heart failure (HF) were observed in 2.4-4.0% from the total sample.

These data provide an informative snapshot of the patient cohort, shedding light on the overall condition and comorbidities of patients that could potentially influence COVID-19 outcomes.

Table 1. Demographic and clinical characteristics data

Characteristic	**Overall**, N = 3647[1]
Age (years)	55 (42, 64)
Sex (% male)	1818 (49.8%)
Length of stay (days)	6.0 (3.0, 10.0)
Level of care (% intensive care)	349 (9.6%)
T2DM without complication (% yes)	852 (23.3%)
Hypertension (% yes)	809 (22%)
Hypoalbuminemia (% yes)	507 (14%)
Renal impairment (% yes)	441 (12%)
Hyponatremia (% yes)	383 (10.5%)
Elevated transaminase levels (% yes)	304 (8.3%)
Anemia (% yes)	266 (7.3%)
Hypokalemia (% yes)	212 (5.8%)
Urinary tract infection(% yes)	190 (5.2%)
Hyperkalemia (% yes)	176 (4.8%)
Upper gastrointestinal bleeding (% yes)	127 (3.5%)
Stroke (% yes)	145 (4.0%)
Coronary arterial disease (% yes)	130 (3.6%)
Heart failure (% yes)	88 (2.4%)
Arrhythmia (% yes)	110 (3.0%)
[1] n (%); Median (IQR)	

Table 2 compares the demographic and clinical characteristics of the patient cohort, segmented by outcome (alive versus deceased). A p-value of less than 0.05 signifies a statistically significant difference between the two groups for that particular characteristic.

The median age of patients who survived was 52 years old (IQR: 37-62), significantly younger than those who deceased, whose median age was 59 years old (IQR: 49-67) ($p < 0.001$). The sex distribution differed significantly between the two groups as well, with a lower proportion of males in the surviving group (47%) compared to the deceased group (53%) ($p<0.001$).

There was a marked difference in the length of hospital stay, with survivors staying longer (median: 7.0 days, IQR: 5.0-11) than those who deceased (median: 4.0 days, IQR: 2.0-8.0) ($p<0.001$). Intensive care was required in 0.4% of survivors versus 23% of deceased patients, a striking difference that was statistically significant ($p<0.001$).

In terms of comorbidities, a higher proportion of deceased patients had type 2 diabetes mellitus without complication (25%) compared to survivors (22%) ($p<0.001$). Hypoalbuminemia, renal impairment and hyponatremia were also significantly more prevalent in the deceased group ($p < 0.001$, $p < 0.001$, and $p = 0.020$, respectively). Elevated transaminase levels were more common in the deceased group as well (13% versus 5.2%, $p = 0.015$).

Notably, upper GIT bleeding was more than twice as prevalent in the deceased group (5.3%) compared to survivors (2.3%), a difference that was statistically significant ($p < 0.001$). Among cardiovascular conditions, heart failure and arrhythmia were significantly more prevalent in the deceased group ($p = 0.005$ and $p < 0.001$, respectively). However, the incidence of hypertension, anemia, hypokalemia, urinary tract infection, stroke, and coronary arterial disease showed no significant statistically differences between the two groups.

These findings highlight the variables that differ significantly between survivors and non-survivors and can be further analyzed as potential predictors of mortality in COVID-19 patients.

In our study examining predictors of mortality in COVID-19 patients, both univariate and multivariate analyses in Table 3 revealed multiple significant variables. Yet, among them, upper gastrointestinal tract bleeding emerged as a particularly crucial predictor, thereby meriting heightened attention.

Table 2. Comparison of demographic and clinical characteristics of the patient cohort, segmented by outcome (alive versus deceased)

Characteristic	**Alive**, N = 2181[1]	**Deceased** N = 1466[1]	**p-value**[2]
Age (years)	52 (37, 62)	59 (49, 67)	<0.001
Sex (% male)	1034 (47%)	784 (53%)	<0.001
Length of stay (days)	7.0 (5.0, 11.0)	4.0 (2.0, 8.0)	<0.001
Level of care (% intensive care)	9 (0.4%)	340 (23%)	<0.001
T2DM without complication (% yes)	478 (22%)	374 (25%)	<0.001
Hypertension (% yes)	636 (29%)	173 (12%)	0.13
Hypoalbuminemia (% yes)	225 (10%)	282 (19%)	<0.001
Renal impairment (% yes)	197 (9.0%)	244 (16%)	<0.001
Hyponatremia (% yes)	208 (9.5%)	175 (12%)	0.020
Elevated transaminase levels (% yes)	114 (5.2%)	190 (13%)	0.015
Anemia (% yes)	194 (8.9%)	72 (4.9%)	0.4
Hypokalemia (% yes)	127 (5.8%)	85 (5.8%)	>0.9
Urinary tract infection(% yes)	112 (5.1%)	78 (5.3%)	0.8
Hyperkalemia (% yes)	56 (2.6%)	120 (8.1%)	<0.001
Upper gastrointestinal bleeding (% yes)	50 (2.3%)	77 (5.3%)	<0.001
Stroke (% yes)	80 (3.7%)	65 (4.4%)	0.2
Coronary arterial disease (% yes)	76 (3.5%)	54 (3.7%)	0.8
Heart failure (% yes)	40 (1.8%)	48 (3.3%)	0.005
Arrhythmia (% yes)	49 (2.2%)	61 (4.2%)	<0.001
[1] n (%); Median (IQR)			
[2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test			

The univariate analysis revealed that, several variables demonstrated a significant relationship with mortality. For instance, type 2 diabetes mellitus raised the odds of death by 56% (OR 1.56, 95% CI 1.34-1.81, p < 0.001), while hypoalbuminemia more than doubled this risk (OR 2.05, 95% CI 1.70-2.48, p < 0.001). Upper gastrointestinal tract bleeding also amplified the odds of death, showing an odds ratio of 2.14 (95% CI 1.48-3.11, p < 0.001). Furthermore, hyperkalemia and renal impairment posed particularly potent threats, tripling the likelihood of death (OR 3.35, 95% CI 2.44-4.67, p < 0.001 and OR 2.91, 95% CI 2.41-3.53, p < 0.001, respectively). Notably, elevated transaminase levels were a significant risk factor (OR 1.29, 95% CI 1.05-1.59, p = 0.015), whereas being female presented a protective effect, reducing the odds of death (OR 0.78, 95% CI 0.69-0.90, p <0.001). Lastly, every additional year of age marginally increased the risk (OR 1.03, 95% CI 1.03-1.04, p < 0.001), while each day in hospital remarkably reduced this risk (OR 0.91, 95% CI 0.89-0.92, p <0.001).

In the multivariate analysis, we factored in the intricate interplay between these variables. Even a midst this complex landscape, upper gastrointestinal tract bleeding steadfastly retained its significance as an independent predictor. When controlled for influential factors like type 2 diabetes mellitus, hypoalbuminemia, renal impairment, age, sex, and length of stay, the presence of upper gastrointestinal tract bleeding still augmented the odds of mortality by 68% (OR 1.68, 95% CI 1.02-2.79, p = 0.042).

Essentially, despite adjusting for several pivotal variables, upper gastrointestinal tract bleeding was consistently associated with a higher risk of death, thereby underscoring its critical role in the prognosis of COVID-19 patients. Our findings stress the need for enhanced vigilance and potentially aggressive interventions to manage patients with this condition and improve their outcomes. Moreover, these results exemplify the necessity for a comprehensive and multifaceted approach when assessing COVID-19 patient prognosis, reflecting the diverse and interconnected nature of this disease and its influences on patient outcomes.

Figure 2 provides a graphical representation of a 30-day survival analysis comparing patients with upper gastrointestinal tract bleeding to those without it, among the COVID-19 patients admitted to RSUP Dr. Sardjito.

The curve for patients with UGIB shows a slight decrease over time, indicating some mortality in this group. Similarly, the curve for patients without UGIB bleeding also decreases, reflecting mortality within this group. However, there does not appear to be a substantial difference between the two curves throughout the 30-day period.

This visual impression is confirmed by the provided p-value of 0.56, which is above the significance threshold of 0.05. This indicates that there is no statistically significant difference in the 30-day survival probabilities of COVID-19 patients with and without UGIB admitted to RSUP Dr. Sardjito.

Table 3. Univariate and multivariate analyses toward several factors as predictors of mortality in COVID-19 patients

Variables	Univariate				Multivariate		
	N	OR [1]	95% CI [1]	p-value	OR [1]	95% CI [1]	p-value
HT							
No	2838	—	—		—	—	
Yes	809	1.12	0.97, 1.29	0.13	0.86	0.71, 1.04	0.13
T2DM							
No	2795	—	—		—	—	
Yes	852	1.56	1.34, 1.81	<0.001	1.44	1.19, 1.75	<0.001
Stroke							
No	3502	—	—		—	—	
Yes	145	1.22	0.87, 1.70	0.2	0.72	0.47, 1.08	0.11
Hypoalbu-minemia							
No	3140	—	—		—	—	
Yes	507	2.05	1.70, 2.48	<0.001	2.20	1.69, 2.88	<0.001
Hyperkale-mia							
No	3471	—	—		—	—	
Yes	176	3.35	2.44, 4.67	<0.001	2.22	1.46, 3.39	<0.001
UTI							
No	3457	—	—		—	—	
Yes	190	1.04	0.77, 1.39	0.8	1.56	1.03, 2.37	0.036
CAD							
No	3517	—	—		—	—	
Yes	130	1.06	0.74, 1.51	0.8	0.59	0.38, 0.93	0.024
Elevated trans-aminase levels							
No	3343	—	—		—	—	
Yes	304	1.29	1.05, 1.59	0.015	1.47	1.13, 1.93	0.005
UGIB							
No	3520	—	—		—	—	
Yes	127	2.14	1.48, 3.11	<0.001	1.68	1.02, 2.79	0.042
Renal impair-ment							
No	3206	—	—		—	—	
Yes	441	2.91	2.41, 3.53	<0.001	2.13	1.66, 2.75	<0.001
Age (years)	3647	1.03	1.03, 1.04	<0.001	1.04	1.03, 1.04	<0.001
Sex							
Male	1818	—	—		—	—	
Female	1829	0.78	0.69, 0.90	<0.001	0.83	0.71, 0.98	0.030
Length of stay	3647	0.91	0.89, 0.92	<0.001	0.82	0.81, 0.84	<0.001
Level of care							
Intensive care	349	—	—		—	—	
Non intensive care	3298	0.01	0.01, 0.03	<0.001	0.00	0.00, 0.01	<0.001
Hyponatre-mia							
No	3264	—	—		—	—	
Yes	383	1.29	1.04, 1.59	0.021			
Hypoka-lemia							
No	3435	—	—		—	—	
Yes	212	1.00	0.75, 1.32	>0.9			
Anemia							
No	3381	—	—		—	—	
Yes	266	1.09	0.90, 1.32	0.4			
HF							
No	3559	—	—		—	—	
Yes	88	1.81	1.19, 2.78	0.006			

[1] OR = Odds Ratio, CI = Confidence Interval

This finding suggests that UGIB did not have a significant impact on the 30-day survival rate in this patient cohort.

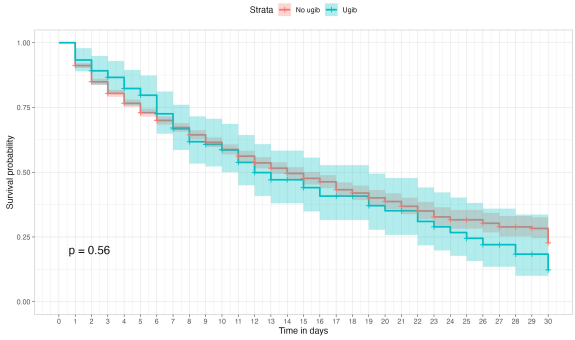

Fig. 2. Representation of a 30-day survival analysis comparing patients with upper gastrointestinal tract bleeding (UGIB) to those without UGIB.

4 Discussion

Our cohort study demonstrated that the median age of patients was 55 years old, with an inter quartile range (IQR) from 42 to 64 years old. The median age of patients who survived was 52 years old (IQR: 37-62), significantly younger than those who deceased, whose median age was 59 years (IQR: 49-67) ($p < 0.001$). Every additional year of age marginally increased the risk (OR 1.03, 95% CI 1.03-1.04, $p < 0.001$). This result can be explained as follows.

The cellular immune system of the aged is compromised on both an innate and adaptive level (immunosenescence), with a pro-inflammatory propensity (inflammaging), which appears to be increased during COVID-19, worsening the disease. [5,6]

An earlier study in 90 healthy people revealed that ciliary disarrangement and nasal mucociliary clearance time increased with age. The increasing incidence and severity of (any) lung infections may be partially explained by these age-related changes, which include

diminished pulmonary reserve and airway clearance. [5,6,7]

Poorer patient outcomes including mortality and morbidity are also linked to higher frailty scores. [6]

Being female presented a protective effect in this study, reducing the odds of death (OR 0.78, 95% CI 0.69-0.90, $p < 0.001$). The sex distribution in this study differed significantly between alive and deceased group with a lower proportion of males in the surviving group (47%) compared to the deceased group (53%) ($p < 0.001$).

Males have 5% fewer heterozygous loci than females due to the fact that they only have one X chromosome. X chromosomal activation may cause variations in the methylation of the ACE2 gene. This finding may help to explain why men are more likely than women to get COVID-19 infection. [5,8,9]

Males with low testosterone levels may be more prone to thromboembolic events in COVID-19 because testosterone is essential for maintaining platelet and coagulation homeostasis. A lack of testosterone may also lead to an increase in the expression of the ACE2 receptor, which makes it easier for SARS-CoV-2 to enter host cells and cause more respiratory failure and lung damage. [8]

Increased estrogen levels have anti-inflammatory effects on endothelial cell function, boost T helper 2 and humoral immune responses, and decrease the pro-inflammatory innate immune response. Furthermore, female patients have higher protective SARS-CoV-2 immunoglobulin G (IgG) antibody levels than male patients do in patients with severe disease, which may help with better clinical outcomes. [8]

The median length of stay in the hospital in this study was six days, ranging between three to ten days. The majority of patients (90.4%) were treated in non-intensive care units, with only 9.6% requiring intensive care. There was a marked difference in the length of hospital stay in this study, with survivors staying longer (median: 7.0 days, IQR: 5.0-11.0) than those who deceased (median: 4.0 days, IQR: 2.0-8.0) ($p < 0.001$). Intensive care was required in 0.4% of survivors versus 23% of deceased patients, a striking difference that was statistically significant ($p < 0.001$). Each day in hospital remarkably reduced this risk (OR 0.91, 95% CI 0.89-0.92, $p < 0.001$).

An earlier study discovered that mild illnesses and longer LOS were related. A possible explanation is that, according to a previous report (SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients), viral loads in symptomatic and asymptomatic patients are equal. The "Diagnosis and Treatment Scheme for Novel Coronavirus Pneumonia (Trial), 6th Edition" in China states that patients with mild disease status were mostly separated from other people and treated with a few symptomatic medications. Nevertheless, the majority of these patients had a high viral load while they were in the hospital. [10]

This study found that a higher proportion of deceased patients had type 2 diabetes mellitus (T2DM) without complication (25%) compared to survivors (22%) ($p < 0.001$), statistically significant. The univariate analysis revealed that type 2 diabetes mellitus raised the odds of death by 56% (OR 1.56, 95% CI 1.34-1.81, $p < 0.001$).

Poor glycaemic management in T2DM patients has been linked in the literature to increased reactive oxygen species (ROS), pro-inflammatory cytokines, and alteration of several immune response components. People with T2DM had higher levels of intracellular furin and an increased expression of angiotensin-converting enzyme-2 (ACE2), a SARS-CoV-2 virus receptor, which made it simpler for the virus to enter cells and multiply, triggering an excessive inflammatory response and raising COVID-19 morbidity and mortality in those with type 2 DM. [11]

As a result, it has been proposed that T2DM may elevate the danger of infection, hospital admission, severe illness, and demise in COVID-19 patients. However, compared to the general population, COVID-19 patients with T2DM had more severe disease and a higher fatality rate. [11,12]

Hypoalbuminemia, renal impairment, and hyponatremia were also significantly more prevalent in the deceased group in this study ($p < 0.001$, $p < 0.001$, and $p = 0.021$, respectively). The univariate analysis revealed that hypoalbuminemia raised the odds of death by more than double (OR 2.05, 95% CI 1.70-2.48, $p < 0.001$). Renal impairment posed particularly potent threats, tripling the likelihood of death (OR 2.91, 95% CI 2.41-3.53, $p < 0.001$). Hyponatremia raised the odds of death by 29% (OR 1.29, 95% CI 1.04-1.59, p 0.021). This result is consistent with the theory and earlier research.

An earlier retrospective analysis found that in COVID-19, a blood albumin level below 35 g/L at presentation independently increased the probability of death by at least six times. [13]

Hypoalbuminemia may therefore be used to assess the severity of epithelial-endothelial damage in COVID-19 patients. Neutrophil extracellular traps (NETs) plays a significant role in mediating tissue damage in inflammatory illnesses including COVID-19. Because serum albumin is known to prevent the development of NETs, this may help to explain why patients with hypoalbuminemia are more likely to experience severe respiratory failure and pass away. [3,14]

Previous study said that among patients with COVID-19 and AKI, high-inflammatory response and severe AKI were associated with significantly higher mortality. Pre-renal AKI is caused by the following factors: COVID-19-related hypovolemia; complement activation; cytokine storm; hypercoagulability; and microangiopathy; nephrotoxic drugs or contrast media; and comorbidities like type 2 diabetes mellitus and hypertension. [15]

According to a different study, pro-inflammatory cytokine levels are up in chronic kidney disease (CKD) patients, and this raises oxidative stress, which then triggers an inflammatory immunological response. [16]

Previous study said that hyponatremia was found to be significantly associated with increased odds for mortality (OR = 1.97 [95% CI, 1.50–2.59]), ICU

admission (OR = 1.91 [95% CI, 1.56–2.35]), assisted ventilation need (OR = 2.04 [95% CI, 1.73–2.38]), and with increased LOS (SMD of 5.74 h [95% CI, 0.092–0.385]).

In a previous study, the most frequently reported causes of hyponatremia among SARS-COV-2 patients were SIADH, adrenal causes and hypovolemia. Although the precise mechanism by which SIADH-induced hyponatremia causes pneumonia is still unknown, one explanation for this is the compensatory hypoxic pulmonary vasoconstriction that results from a ventilation perfusion mismatch. [17]

Furthermore, hyperkalemia posed particularly potent threats, tripling the likelihood of death in this study (OR 3.35, 95% CI 2.44-4.67, $p < 0.001$).

SARS-CoV-2 can lead to both decreases and increases in serum potassium levels. Previous study said that compared to patients with COVID-19 who had a Ka+ level of 4.0 to 4.5 mmol/L, those with a Ka+ level 5.0 mmol/L had a significantly higher 30-day mortality. [18]

According to a systematic review and meta-analysis, patients with acute myocardial infarction had a greater risk of death for serum potassium levels that are both lower (3.5 mEq/L) and higher (4.5 mEq/L). Acid-base balance problems may have aberrant plasma potassium as one of its symptoms, which signals severe acute respiratory distress syndrome. [18]

Elevated transaminase levels occurred in 8.3% of the total patients in this study. Elevated transaminase levels were slightly more common in the deceased group in this study as well (13% versus 5.2%, $p = 0.015$). This phenomenon can be explained as follows.

The direct liver injury, related inflammatory responses, congestive hepatopathy, hepatic ischemia, drug-induced liver injury (DILI), and muscle breakdown are just a few possible contributory etiologies to increased liver enzymes in SARS-CoV-2 patients. [19]

Bile duct and liver epithelial cells also express ACE2, making it simple for SARS-CoV-2 to bind to ACE2-positive cholangiocytes and impair liver function. [20]

In this study, upper GIT bleeding was detected in 3.5% of cases. Upper gastrointestinal bleeding increased the risk of mortality in univariate analysis, with an odds ratio of 2.14 in this study.

The presence of upper gastrointestinal bleeding still augmented the odds of mortality by 68% when influential factors like type 2 diabetes mellitus, hypoalbuminemia, renal impairment, age, sex, and length of stay were controlled (OR 1.68, 95% CI 1.02-2.79, $p = 0.042$). Fundamentally, upper gastrointestinal bleeding was continuously linked to an increased probability of death, highlighting its crucial significance in COVID-19 patients' prognosis.

Some writers proposed that, in addition to the direct effects of the virus on the gastrointestinal mucosa, bleeding may also result through the development of an inflammation-induced coagulopathy and thromboinflammation. [2]

Due to the fact that the brush border of intestinal enterocytes expresses angiotensin-converting enzyme 2 at the highest level in the human body—the viral binding site—SARS CoV-2 is able to infect enteric cells. In the cytoplasm of gastric, duodenal, and rectal cells from COVID-19 patients who had SARS-COV-2 fecal shedding, SARS CoV-2 nucleocapsid proteins were found. Infection with SARS-CoV-2 resulted in inflammation of the gastrointestinal mucosa and a decrease in the functional mass of epithelial cells. Since bleeding mostly happened while patients were in hospitals, a complex explanation has been proposed. [2]

The majority of COVID-19 patients with symptoms used anticoagulants such as heparin, at least in preventive dosages, to prevent prothrombotic activity linked to COVID-19. Additionally, elevated levels of D-dimer and fibrinogen caused by the COVID-19-associated coagulopathy, which may raise the risk of thrombosis and explain the development of ischemic colitis, might cause gastrointestinal bleeding. Other possible causes of gastrointestinal bleeding in COVID-19 individuals include ulcers that develop during periods of extreme stress, including hospitalization, or disseminated intravascular coagulation, a hypercoagulable illness that also causes bleeding.[2]

Previous meta analysis suggested that the incidence of occult gastrointestinal bleeding was significantly higher in severe patients, probably as a result of stress-related mucosal disease (SRMD) in severe cases. SRMD can result from hypotension, hypovolaemia, elevated catecholamine levels, the release of pro-inflammatory cytokines, vasoconstriction, or hypotension. [3]

Coagulopathy has been identified as a risk factor for gastrointestinal bleeding. Prolonged PT may exacerbate gastrointestinal bleeding brought on by mucosal injury. Two crucial host defensive mechanisms are coagulation and a rise in the inflammatory response as the disease progresses, which could harm the host. In COVID-19 individuals, irregular coagulation is linked to a higher risk of death. [3]

In a recent study, autopsy results of COVID-19 patients revealed characteristic platelet-rich thrombus deposits in the tiny arteries of the lungs and other organs. It implies that the coagulopathy linked to COVID-19 is a fusion of localized pulmonary thrombotic microangiopathy and low-grade disseminated intravascular coagulation, which may have a major effect on organ functioning. [3]

In critically ill patients, cytokine storms characterized by high concentrations of proinflammatory cytokines and chemokines can be observed, and the release of tumor necrosis factor (TNF α) and interleukin can affect coagulation function. [3]

Nevertheless, this study found that there is no statistically significant difference in the 30-day survival probabilities of COVID-19 patients with and without upper GIT bleeding admitted to RSUP Dr. Sardjito (p-value 0.56). This result is possible because 30-day survival probabilities of COVID-19 patients are influenced by many factors, not just the incidence of upper GI tract bleeding. Age, sex, severity of COVID-19, accompanying comorbidities as explained above, greatly affect survival probabilities. These results exemplify the necessity for a comprehensive and

multifaceted approach when assessing COVID-19 patient prognosis, reflecting the diverse and interconnected nature of this disease and its influences on patient outcomes.

Our study has some limitations including the retrospective design of the study which may have introduced bias in the study results. Secondly, the number of patients with upper GI tract bleeding is small in our study, and we suggest that larger studies need to be carried out in future. Thirdly, our study lacked data on drug use before and during COVID-19 treatment. Fourth, patients with COVID-19 were unable to perform comprehensive gastrointestinal examination to clarify gastrointestinal mucous damage and bleeding owing to the restriction of clinical conditions.

5 Conclusion

Upper gastrointestinal bleeding still augmented the odds of mortality by 68% (OR 1.68, 95% CI 1.02-2.79, p = 0.042) when influential factors like type 2 diabetes mellitus, hypoalbuminemia, renal impairment, age, sex, and length of stay were controlled. Nevertheless, there is no statistically significant difference in the 30-day survival probabilities of COVID-19 patients with and without upper GIT bleeding admitted to RSUP Dr. Sardjito (p-value 0.56)

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