RESEARCH ARTICLE

WILEY

In-hospital mortality in SARS-CoV-2 stratified by gamma-glutamyl transferase levels

Moudhi Alroomi[1] | Rajesh Rajan[2] | Ahmad Alsaber[3] | Jiazhu Pan[3] |
Mohammed Abdullah[1] | Hassan Abdelnaby[4,5] | Wael Aboelhassan[6] | Noor AlNasrallah[7] |
Bader Al-Bader[8] | Haya Malhas[9] | Maryam Ramadhan[10] | Soumoud Hussein[11] |
Naser Alotaibi[7] | Mohammad Al Saleh[8] | Kobalava D. Zhanna[12] | Farah Almutairi[8]

[1]Department of Infectious Diseases, Infectious Diseases Hospital, Shuwaikh Medical Area, Kuwait

[2]Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City, Kuwait

[3]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

[4]Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[5]Division of Gastroenterology, Department of Medicine, Al Sabah Hospital, Shuwaikh Medical Area, Kuwait

[6]Division of Gastroenterology, Department of Medicine, Jaber Al Ahmed Hospital, South Surra, Kuwait

[7]Department of Medicine, Al Adan Hospital, Hadiya, Kuwait

[8]Department of Medicine, Farwaniya Hospital, Farwaniya, Kuwait

[9]Department of Medicine, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

[10]Department of Obstetrics and Gynaecology, Maternity Hospital, Shuwaikh Medical Area, Kuwait

[11]Department of Medicine, Al Amiri Hospital, Kuwait City, Kuwait

[12]Department of Internal Medicine with the Subspecialty of Cardiology and Functional Diagnostics Named after V.S. Moiseev, Institute of Medicine, Peoples' Friendship University of Russia (RUDN University), Moscow, Russian Federation

Correspondence
Rajesh Rajan, Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City 15003, Kuwait.
Email: cardiology08@gmail.com

Abstract

Background: This study investigates in-hospital mortality amongst patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its relation to serum levels of gamma-glutamyl transferase (GGT).

Methods: Patients were stratified according to serum levels of gamma-glutamyl transferase (GGT) (GGT<50 IU/L or GGT≥50 IU/L).

Results: A total of 802 participants were considered, amongst whom 486 had GGT<50 IU/L and a mean age of 48.1 (16.5) years, whilst 316 had GGT≥50 IU/L and a mean age of 53.8 (14.7) years. The chief sources of SARS-CoV-2 transmission were contact (366, 45.7%) and community (320, 40%). Most patients with GGT≥50 IU/L had either pneumonia (247, 78.2%) or acute respiratory distress syndrome (ARDS) (85, 26.9%), whilst those with GGT<50 IU/L had hypertension (141, 29%) or diabetes mellitus (DM) (147, 30.2%). Mortality was higher amongst patients with GGT≥50 IU/L (54, 17.1%) than amongst those with GGT<50 IU/L (29, 5.9%). More patients with GGT≥50 required high (83, 27.6%) or low (104, 34.6%) levels of oxygen, whereas most of those with GGT<50 had no requirement of oxygen (306, 71.2%). Multivariable logistic

regression analysis indicated that GGT≥50 IU/L (odds ratio [OR]: 2.02, 95% confidence interval [CI]: 1.20–3.45, p=0.009), age (OR: 1.05, 95% CI: 1.03–1.07, p<0.001), hypertension (OR: 2.06, 95% CI: 1.19–3.63, p=0.011), methylprednisolone (OR: 2.96, 95% CI: 1.74–5.01, p<0.001) and fever (OR: 2.03, 95% CI: 1.15–3.68, p=0.016) were significant predictors of all-cause cumulative mortality. A Cox proportional hazards regression model (B = −0.68, SE =0.24, HR =0.51, p = 0.004) showed that patients with GGT<50 IU/L had a 0.51-times lower risk of all-cause cumulative mortality than patients with GGT≥50 IU/L.

Conclusion: Higher levels of serum GGT were found to be an independent predictor of in-hospital mortality.

KEYWORDS
COVID-19, gamma-glutamyl transferase, in-hospital mortality, SARS-CoV-2

1 | INTRODUCTION

Amongst cases of coronavirus disease (COVID-19), 60% of patients have deranged liver diseases.[1] Many studies have shown that 2–11% of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have an underlying liver disease.[2] In SARS-CoV-2, deranged liver function is considered a marker of the severity of the disease.[3–5] Gamma-glutamyl transferase (GGT) is considered a specific diagnostic biomarker of hepatic cholangiocytic activity.[6,7] SARS-CoV-2-related liver injury in relation to cholangiocytic activity can be assessed by analysing GGT serum levels.[8] GGT levels are elevated in SARS-CoV-2 infection,[2] which is mostly attributed to the immune-mediated response and cytotoxicity.[9,10]

2 | METHODS

2.1 | Study design and subjects

This study examined 802 patients with confirmed SARS-CoV-2 infection, including both Kuwaitis and non-Kuwaitis aged 18 years or older. Patients were enrolled in this retrospective cohort study between 26 February and 8 September 2020. [Figure 1.] All the data were obtained from electronic medical records from two tertiary care hospitals in Kuwait: Jaber Al-Ahmed Hospital and Al Adan General Hospital.[11-13] An electronic case-record form (CRF) was used for data entry.

SARS-CoV-2 infection was confirmed by a positive result of reverse transcription-polymerase chain reaction (RT-PCR) using a swab of the nasopharynx. The care of all patients was standardized according to a protocol established by the Ministry of Health in Kuwait. SARS-CoV-2 patients were stratified according to serum levels of GGT (GGT<50 IU/L and GGT≥50 IU/L). The Standing Committee For the Coordination of Health and Medical Research at the Ministry of Health in Kuwait waived the requirement of informed consent and approved the study (Institutional review board number 2020/1422).

GGT measurement was carried out in biochemistry laboratories in Jaber Al-Ahmed and Al Adan General Hospitals. Patient serum and plasma samples were handled by the laboratory technicians. Quantitative measurement of GGT is reported by Beckman Coulter AU analysers, which is a kinetic colour test. Method of the machine based on the guidelines of the International Federation for Clinical Chemistry (IFCC). The lowest measurable value of the test, representing the tests' sensitivity, was approximated at 2 U/L. Estimates of precision are according to Clinical and Laboratory Standards Institute (CLSI) guidance; the coefficient of variation was less than 5%.
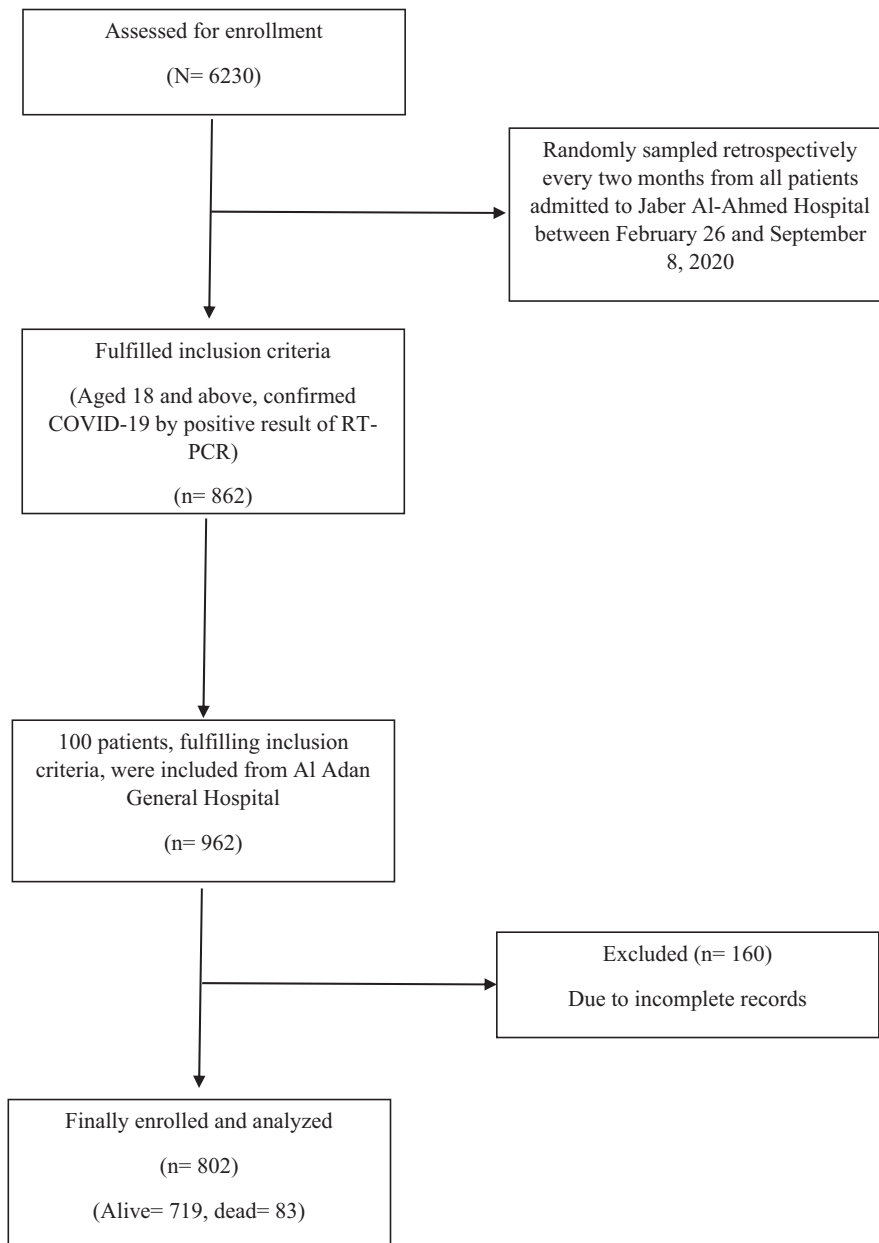
According to the study hospital protocol, biochemistry laboratory results would usually be reported in the electronic medical records on the first days of admission. Blood samples were collected by a nurse on the same day of the report. We documented this one-time point result for each study participant admitted with a confirmed COVID-19 diagnosis. Hence, the GGT results in our study reflect the baseline laboratory profile. Our study analysed GGT on admission as a predictor for COVID-19-related mortality. Other GGT-related predictors, such as those related to the treatment effect or effect of hospitalization, were beyond the scope of the study.

2.2 | Definitions

The primary outcome measured was SARS-CoV-2-related mortality as defined by ICD-10 code U07.1. The secondary outcome measures were the duration of hospital stay and the need for admission to the intensive care unit (ICU). The following clinical and laboratory variables were collected: sociodemographic determinants, comorbidities, clinical presentations, laboratory results, medications received in hospital, oxygen requirement and durations of ICU and in-hospital stays.

Patients with a confirmed diagnosis of restrictive or obstructive disease were considered in the chronic lung disease category. The immunosuppression category was defined as patients on immunosuppressive therapy. The requirement of oxygen was considered

FIGURE 1 Study flowchart

```
┌─────────────────────────────┐
│   Assessed for enrollment   │
│        (N= 6230)            │
└─────────────────────────────┘
              │
              │         ┌──────────────────────────────────┐
              ├────────→│ Randomly sampled retrospectively  │
              │         │ every two months from all patients│
              │         │ admitted to Jaber Al-Ahmed Hospital│
              │         │ between February 26 and September  │
              │         │             8, 2020               │
              │         └──────────────────────────────────┘
              ↓
┌─────────────────────────────┐
│  Fulfilled inclusion criteria│
│  (Aged 18 and above, confirmed│
│   COVID-19 by positive result│
│      of RT-PCR)             │
│        (n= 862)             │
└─────────────────────────────┘
              ↓
┌─────────────────────────────┐
│ 100 patients, fulfilling     │
│ inclusion criteria, were     │
│ included from Al Adan        │
│ General Hospital             │
│        (n= 962)             │
└─────────────────────────────┘
              │
              │         ┌──────────────────────────────────┐
              ├────────→│      Excluded (n= 160)            │
              │         │   Due to incomplete records       │
              │         └──────────────────────────────────┘
              ↓
┌─────────────────────────────┐
│  Finally enrolled and analyzed│
│        (n= 802)             │
│   (Alive= 719, dead= 83)    │
└─────────────────────────────┘
```

'none', 'low', or 'high'. Patients who were on oxygen via a nasal cannula or a nonrebreather mask were classified as the low requirement category. Those who required extracorporeal membrane oxygenation (ECMO), invasive ventilation, noninvasive ventilation or high-flow oxygen were grouped in the high requirement category.

2.3 | Statistical analysis

Descriptive statistics were used to summarize the data in the form of the frequency, percentage, mean ± standard deviation (SD) and median ±interquartile range (IQR). Pearson's χ^2 test was performed to determine the factors associated with the GGT cohorts (GGT<50 IU/L, GGT≥50 IU/L). Multivariable logistic regression was used to check the impacts of GGT, age, hypertension, methylprednisolone and fever on mortality. The relationship between GGT (GGT<50 IU/L, GGT≥50 IU/L) and mortality was assessed using Cox regression analysis and a Kaplan–Meier survival curve. An alpha level of 5% was used to check the significance of the results. SPSS version 27 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) were used to conduct the statistical analyses of the data.[14]

3 | RESULTS

The baseline characteristics of the COVID-19 patients are shown in Table 1. A total of 802 hospitalized patients were enrolled in the study and stratified based on GGT<50 IU/L and GGT≥50 IU/L. The ratio of females to males was 297:504. The average age of patients with GGT≥50 IU/L was 53.8 ± 14.7 years, opposed to that of patients with GGT <50 IU/L (48.1 ± 16.5 years).

TABLE 1 Baseline characteristics of COVID-19 patients stratified by serum GGT levels

	[ALL] N = 802	GGT <50 IU/L N = 486	GGT ≥50 IU/L N = 316	p value	N
Age, mean ± SD, years	50.3 (16.0)	48.1 (16.5)	53.8 (14.7)	<0.001	802
BMI, mean ± SD, kg/m²	29.2 (6.47)	28.8 (6.65)	29.9 (6.09)	0.090	482
Sex:					
Female	297 (37.1%)	193 (39.8%)	104 (32.9%)	0.058	801
Male	504 (62.9%)	292 (60.2%)	212 (67.1%)		
Smoking:					
Current smoker	31 (19.5%)	21 (20.2%)	10 (18.2%)	0.898	159
Ex-smoker	16 (10.1%)	11 (10.6%)	5 (9.09%)		
Never smoked	112 (70.4%)	72 (69.2%)	40 (72.7%)		
Source of transmission:					
Community	320 (40.0%)	160 (32.9%)	160 (50.8%)	<0.001	801
Contact	366 (45.7%)	236 (48.6%)	130 (41.3%)		
Health care worker	22 (2.75%)	14 (2.88%)	8 (2.54%)		
Hospital acquired	11 (1.37%)	5 (1.03%)	6 (1.90%)		
Imported	82 (10.2%)	71 (14.6%)	11 (3.49%)		
Hypertension	274 (34.2%)	141 (29.0%)	133 (42.1%)	<0.001	802
DM	273 (34.0%)	147 (30.2%)	126 (39.9%)	0.006	802
CVD	66 (8.23%)	46 (9.47%)	20 (6.33%)	0.148	802
Chronic lung disease	72 (8.98%)	38 (7.82%)	34 (10.8%)	0.195	802
Chronic kidney disease	40 (4.99%)	21 (4.32%)	19 (6.01%)	0.363	802
Immunocompromised host	15 (1.87%)	6 (1.23%)	9 (2.85%)	0.167	802
Pneumonia	444 (55.4%)	197 (40.5%)	247 (78.2%)	<0.001	802
ARDS	128 (16.0%)	43 (8.85%)	85 (26.9%)	<0.001	802
ICU admission	131 (16.3%)	44 (9.05%)	87 (27.5%)	<0.001	802
ICU duration of stay (days) IQR	14.0 [2.00;65.2]	14.0 [2.00;66.2]	13.5 [1.18;62.0]	0.615	132
Admission to discharge (days) IQR	16.0 [3.00;52.2]	16.0 [3.00;49.0]	17.0 [3.00;60.8]	0.028	793
Mortality	83 (10.3%)	29 (5.97%)	54 (17.1%)	<0.001	802

Note: The values are *n* (%) unless specified otherwise.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease; CVD, cardiovascular disease; DM, diabetes mellitus; GGT, gamma-glutamyl transferase; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

The key source of COVID-19 transmission amongst patients was either the community (320, 40%) or direct contact (366, 45.7%). More patients with GGT<50 IU/L (236, 48.6%) were affected by COVID-19 due to contact than patients with GGT ≥50 IU/L (130, 41.3%). It is worth noting that more patients with GGT ≥50 IU/L had pneumonia (247, 78.2%) and acute respiratory distress syndrome (ARDS) (85, 26.9%), whereas those with GGT<50 IU/L had higher rates of hypertension (141, 29%) and diabetes mellitus (DM) (147, 30.2%).

More patients with GGT ≥50 IU/L had to be admitted to the ICU than patients with GGT<50 IU/L. The mortality rate of patients with GGT ≥50 IU/L (54, 17.1%) was also higher than that of patients with GGT<50 IU/L (29, 5.9%). The major significant symptoms (*p* < 0.001) of patients with higher GGT levels were fever (227, 71.8%) and shortness of breath (132, 41.8%), whilst those of patients with lower GGT levels were no symptoms (119, 24.5%) and dry cough (203, 41.8%) (Table 2).

Compared to the patients with GGT<50 IU/L, those with GGT≥50 IU/L had significantly higher platelet, white blood cell (WBC) and neutrophil counts and creatinine, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, high-sensitivity (HS) serum troponin, ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin and direct bilirubin levels. Moreover, patients with lower GGT (GGT<50 IU/L) had significantly higher lymphocyte counts and albumin levels (Table 3).

Significantly more patients with GGT ≥50 IU/L had received antibiotics (214, 67.7%), methylprednisolone (84, 26.6%), dexamethasone (39, 12.3%), therapeutic anticoagulation (138, 43.7%), azithromycin (12, 3.8%), hydroxychloroquine (66, 20.9%), kaletra (lopinavir/

TABLE 2 Signs and symptoms of COVID-19 stratified by serum GGT levels

	[ALL]	GGT <50 IU/L	GGT ≥50 IU/L	p value	N
	N = 802	N = 486	N = 316		
Asymptomatic	138 (17.2%)	119 (24.5%)	19 (6.01%)	<0.001	802
Headache	91 (11.3%)	56 (11.5%)	35 (11.1%)	0.935	802
Sore throat	82 (10.2%)	52 (10.7%)	30 (9.49%)	0.666	802
Fever	448 (55.9%)	221 (45.5%)	227 (71.8%)	<0.001	802
Dry cough	385 (48.0%)	203 (41.8%)	182 (57.6%)	<0.001	802
Productive cough	48 (5.99%)	29 (5.97%)	19 (6.01%)	>0.999	802
SOB	229 (28.6%)	97 (20.0%)	132 (41.8%)	<0.001	802
Fatigue or myalgia	182 (22.7%)	107 (22.0%)	75 (23.7%)	0.630	802
Diarrhoea	106 (13.2%)	67 (13.8%)	39 (12.3%)	0.629	802
Nausea	55 (6.86%)	28 (5.76%)	27 (8.54%)	0.167	802
Vomiting	50 (6.23%)	27 (5.56%)	23 (7.28%)	0.403	802
Change of taste or smell	29 (3.62%)	22 (4.53%)	7 (2.22%)	0.129	802

Note: The values are n (%) unless specified otherwise.

Abbreviations: COVID-19, coronavirus disease; GGT, gamma-glutamyl transferase; SOB, shortness of breath.

TABLE 3 Laboratory findings of COVID-19 patients stratified by serum GGT levels

	[ALL]	GGT <50 IU/L	GGT ≥50 IU/L	p value	N
	N = 802	N = 486	N = 316		
Haemoglobin (g/L)	130 [128;131]	131 [128;133]	129 [123;131]	0.061	798
Platelets (10^9/L)	259 [250;269]	250 [238;261]	279 [262;289]	0.009	797
WBC (10^9/L)	6.70 [6.50;7.00]	6.20 [5.90;6.50]	7.65 [7.10;8.30]	<0.001	796
Neutrophils count	4.10 [3.90;4.40]	3.60 [3.30;3.80]	5.50 [4.90;6.10]	<0.001	795
Lymphocytes count	1.50 [1.40;1.60]	1.70 [1.50;1.80]	1.20 [1.00;1.40]	<0.001	795
Creatinine (umol/L)	76.0 [74.0;77.0]	73.0 [71.0;75.0]	81.0 [77.0;84.0]	<0.001	793
LDH (IU/L)	290 [274;306]	246 [231;270]	344 [322;366]	<0.001	511
CRP (mg/L)	40.5 [32.0;52.0]	17.0 [13.0;21.0]	87.0 [77.0;99.0]	<0.001	760
Procalcitonin (ng/mL)	0.08 [0.07;0.10]	0.06 [0.05;0.07]	0.24 [0.18;0.41]	<0.001	491
D-Dimer (ng/mL)	354 [311;410]	264 [250;321]	467 [395;518]	<0.001	502
25 (OH) Vitamin D (nmol/L)	40.0 [37.0;44.0]	41.0 [37.0;45.0]	38.0 [32.0;47.0]	0.454	224
Troponin I HS (ng/L)	9.00 [8.00;12.0]	7.00 [6.00;12.0]	10.0 [8.00;15.0]	0.007	308
Ferritin (ng/mL)	426 [387;473]	322 [282;390]	536 [454;659]	<0.001	477
Creatinine kinase (IU/L)	82.5 [59.0;125]	81.0 [42.0;208]	88.0 [55.0;178]	0.765	28
ALT (IU/L)	32.0 [30.0;35.0]	25.0 [23.0;26.0]	58.0 [51.0;66.0]	<0.001	802
AST (IU/L)	32.0 [30.0;33.0]	26.0 [24.0;27.0]	49.2 [47.0;54.0]	<0.001	802
ALP (IU/L)	69.0 [66.0;71.0]	61.0 [60.0;63.0]	87.0 [83.0;92.0]	<0.001	801
Albumin (g/L)	34.9 [34.1;35.3]	36.0 [35.4;36.8]	32.7 [31.8;33.5]	<0.001	799
T. Bilirubin (umol/L)	11.7 [11.3;12.1]	11.2 [10.5;11.6]	12.9 [12.0;13.9]	<0.001	802
D. Bilirubin (umol/L)	2.40 [2.30;2.50]	2.12 [2.00;2.20]	3.00 [2.80;3.30]	<0.001	800

Note: The values are median [IQR].

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease; CRP, C-reactive protein; D. bilirubin, direct bilirubin; GGT, gamma-glutamyl transferase; HS, high-sensitivity; LDH, lactate dehydrogenase; T. bilirubin, total bilirubin; WBC, white blood cells.

ritonavir) (56, 17.7%), hydrocortisone (14, 4.4%) and current use of ACE inhibitors (39, 14.7%) than the patients with GGT<50 IU/L. Moreover, more patients with GGT≥50 IU/L required either high (83, 27.6%) or low levels of oxygen (104, 34.6%). More patients with GGT<50 IU/L had no requirement for oxygen (306, 71.2%) (Table 4).

The impact of GGT, age, hypertension, methylprednisolone and fever on cumulative all-cause mortality was assessed using a multivariable logistic regression model (Table 5). Multivariable analysis showed that GGT ≥50 IU/L (odds ratio [OR]: 2.02, 95% confidence interval [CI]: 1.20–3.45, $p = 0.009$), age (OR: 1.05,

95% CI: 1.03–1.07, $p < 0.001$), hypertension (OR: 2.06, 95% CI: 1.19–3.63, $p = 0.011$), methylprednisolone (OR: 2.96, 95% CI: 1.74–5.01, $p < 0.001$) and fever (OR: 2.03, 95% CI: 1.15–3.68, $p = 0.016$) were significantly associated with cumulative all-cause mortality in COVID-19 patients (Table 5). A Cox proportional hazards model was conducted to determine whether GGT had a significant effect on the hazard of mortality (Table 6). The 'no' category of mortality was used to indicate survival, whilst the 'yes' category was used to represent a hazard event. The results of the model were significant based on an alpha value of 0.05,

TABLE 4 Medications administered to COVID-19 patients stratified by serum GGT levels

| | [ALL] | GGT <50 IU/L | GGT ≥50 IU/L | p value | N |
	N = 802	N = 486	N = 316		
Antibiotics	365 (45.5%)	151 (31.1%)	214 (67.7%)	<0.001	802
Methylprednisolone	130 (16.2%)	46 (9.47%)	84 (26.6%)	<0.001	802
Dexamethasone	60 (7.48%)	21 (4.32%)	39 (12.3%)	<0.001	802
Vitamin C effervescent tablets	571 (71.2%)	354 (72.8%)	217 (68.7%)	0.232	802
Therapeutic anticoagulation	233 (29.1%)	95 (19.5%)	138 (43.7%)	<0.001	802
Azithromycin	18 (2.24%)	6 (1.23%)	12 (3.80%)	0.032	802
Vitamin D:					
With Vit-D	299 (37.3%)	193 (39.7%)	106 (33.5%)	0.091	802
Without Vit-D	503 (62.7%)	293 (60.3%)	210 (66.5%)		
Hydroxychloroquine	111 (13.8%)	45 (9.26%)	66 (20.9%)	<0.001	802
Kaletra (lopinavir/ritonavir)	108 (13.5%)	52 (10.7%)	56 (17.7%)	0.006	802
Tocilizumab	12 (1.50%)	4 (0.82%)	8 (2.53%)	0.072	802
Hydrocortisone	19 (2.37%)	5 (1.03%)	14 (4.43%)	0.004	802
Receiving ACE inhibitors	70 (10.5%)	31 (7.71%)	39 (14.7%)	0.006	667
Receiving ARBs	100 (15.0%)	54 (13.5%)	46 (17.2%)	0.234	668
Receiving statin	192 (27.6%)	107 (25.5%)	85 (30.7%)	0.161	696
Oxygen requirements:					
High oxygen requirement	125 (17.1%)	42 (9.77%)	83 (27.6%)	<0.001	731
Low oxygen requirements	186 (25.4%)	82 (19.1%)	104 (34.6%)		
None	420 (57.5%)	306 (71.2%)	114 (37.9%)		

Note: The values are n (%), unless specified otherwise.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COVID-19, coronavirus disease; GGT, gamma-glutamyl transferase.

TABLE 5 Logistic regression analysis of risk factors for in-hospital death in the overall study cohort

| Mortality		Alive	Dead	Crude OR (95% CI, p value)	Adjusted OR (95% CI, p value)
GGT (IU/L)	GGT ≥50	262 (82.9)	54 (17.1)	3.25 (2.03–5.29, $p < 0.001$)	2.02 (1.20–3.45, $p = 0.009$)
Age (n, years)	Mean (SD)	48.8 (15.4)	63.5 (15.1)	1.06 (1.05–1.08, $p < 0.001$)	1.05 (1.03–1.07, $p < 0.001$)
Hypertension	Yes	217 (79.2)	57 (20.8)	5.07 (3.14–8.40, $p < 0.001$)	2.06 (1.19–3.63, $p = 0.011$)
Methylprednisolone	Yes	93 (71.5)	37 (28.5)	5.41 (3.33–8.79, $p < 0.001$)	2.96 (1.74–5.01, $p < 0.001$)
Fever	Yes	387 (86.4)	61 (13.6)	2.38 (1.45–4.04, $p = 0.001$)	2.03 (1.15–3.68, $p = 0.016$)

Note: The percentages are raw percentages. Multivariable logistic regression analysis was conducted using the simultaneous method. The model was adjusted for GGT, age, hypertension, methylprednisolone use and fever.

Abbreviations: CI, confidence interval; GGT, gamma-glutamyl transferase; OR, odds ratio; SD, standard deviation.

TABLE 6 Cox Proportional Hazards Regression Coefficients for GGT

Variable	B	SE	95% CI	z	p	HR
GGT:GGT<50	−0.68	0.24	[−1.14, −0.22]	−2.89	0.004	0.51

FIGURE 2 Kaplan–Meier survival plot of mortality according to GGT levels in patients with coronavirus disease [COVID-19]. X-axis: Days since admission
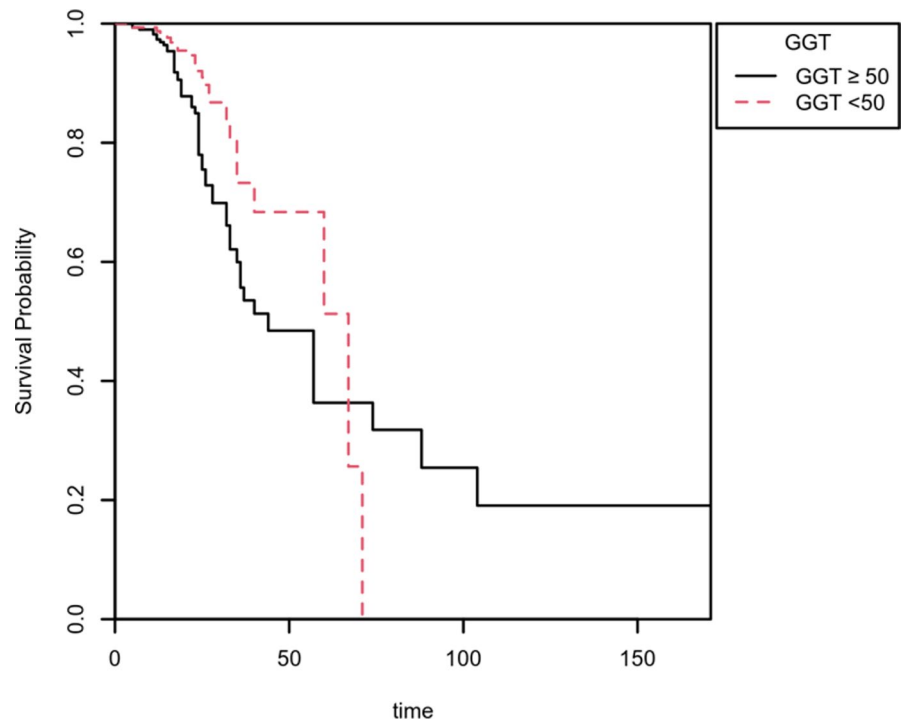
LL =8.70, df =1 and p = 0.003, indicating that GGT was able to adequately predict the hazard of mortality. The coefficients for GGT (B = −0.68, SE =0.24, HR =0.51, p = 0.004) indicate the patients with GGT<50 IU/L had a 0.51-times lower risk of mortality than the patients with GGT≥50 IU/L.

Kaplan–Meier survival probability plots were obtained for GGT. Each plot represents the survival probabilities for different groups over time. The Kaplan–Meier survival analysis showed that the cumulative probability of dying in the initial period was higher for patients with GGT≥50 IU/L. [Figure 2].

4 | DISCUSSION

Our study is one of the first to concentrate on in-hospital mortality in SARS-CoV-2 in specific relation to serum GGT levels. The main finding of our study is that higher levels of serum GGT (≥50 IU/L) were an independent predictor of in-hospital mortality. Other than serum GGT levels, age, hypertension, methylprednisolone use and fever were found to be predictors of in-hospital mortality. There were more elderly patients with GGT≥50 IU/L. ICU admissions were also higher with GGT≥50 IU/L.

Other variables of liver function tests, such as ALP and ALT, were also elevated with GGT levels. The chief source of transmission of SARS-CoV-2 amongst the patients was contact (366, 45.7%) or the community (320, 40%). Most patients with GGT≥50 IU/L had either pneumonia or ARDS. Those with GGT≥50 U/L more often required high or low levels of oxygen.

Abnormal GGT levels during admission predict worse outcomes in critically ill SARS-CoV-2 patients.[15,16] Higher levels of GGT were associated with elderly patients.[17] The severity of SARS-CoV-2 has been observed to be higher in elderly men who have elevated GGT levels.[18] Worse SARS-CoV-2-related prognoses and outcomes have been reported in a male cohort with elevated GGT.[19] Elevated GGT and CRP have strong interactions with the outcomes of SARS-CoV-2.[20] Elevated GGT is mostly seen in association with elevated ALP and AST in SARS-CoV-2.[21]

ICU admissions have been seen more often in SARS-CoV-2 patients with elevated serum GGT levels.[18] Higher mortality has been reported in patients who were previously known to have had liver disease.[22,23] One-month mortality was seen to be higher in SARS-CoV-2 patients with cirrhosis.[24] Altered levels of GGT have been seen in SARS-CoV-2 patients and are associated with longer hospital stays.[25-27]

4.1 | Limitations

Our study has various limitations. Unmeasured confounding factors, such as clinical comorbidities and medications, could have affected the outcomes. This Kuwaiti study included all the SARS-CoV-2-positive patients.

5 | CONCLUSIONS

This study demonstrated that serum GGT≥50 IU/L is an independent predictor of in-hospital mortality in SARS-CoV-2 patients. The incidence of ICU admission was higher with elevated serum GGT levels. More prospective studies are required to better understand the role of serum GGT levels in predicting in-hospital mortality in COVID-19.

CONFLICT OF INTEREST

No conflict of interest to disclose for any author on this manuscript.

AUTHOR CONTRIBUTIONS

MAR designed the study. MAR and RR participated in data analysis and wrote the manuscript. AAS and JP performed the statistical analysis and reviewed the manuscript. The remaining authors collected the data. All authors had access to the data and took responsibility for the integrity and accuracy of data analysis. All authors have read and approved the manuscript. The authors thank Dr Danah Alothman, Dr Mohamed Elmetwalli Ghazi, and Dr Dhari Alown for their support in manuscript review.

PATIENT CONSENT STATEMENT

The requirement for patient consent was waived because of the retrospective observational study design.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material from other sources was included in this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

ORCID

Moudhi Alroomi https://orcid.org/0000-0001-6907-011X
Rajesh Rajan https://orcid.org/0000-0002-0249-0440

REFERENCES

1. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. *Hepatology*. 2020;72:807-817. 10.1002/hep.31404
2. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020;5:428-430.
3. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. *J Hepatol*. 2020;73(3):566-574. 10.1016/j.jhep.2020.04.006
4. Xie H, Zhao J, Lian N, et al. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. *Liver Int*. 2020;40(6):1321-1326. 10.1111/liv.14449
5. Fan Z, Chen L, Li J, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. *Clin Gastroenterol Hepatol*. 2020;18(7):1561-1566. 10.1016/j.cgh.2020.04.002. Epub 2020 Apr 10. PMID: 32283325; PMCID: PMC7194865.
6. Hanigan MH, Frierson HF Jr. Immunohistochemical detection of gamma-glutamyl transpeptidase in normal human tissue. *J Histochem Cytochem*. 1996;44:1101-1108.
7. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci*. 2001;38:263-355.
8. Saini N, Saini RK, Kumari M, et al. Evaluation of gamma glutamyltransferase (GGT) levels in COVID-19: a retrospective analysis in tertiary care centre. *Indian J Biochem Biophys*. 2020;57(6):681-686.
9. Wang Y, Liu S, Liu H, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol*. 2020;73:807-816.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475-481.
11. Al-Jarallah M, Rajan R, Saber AAL, et al. In-hospital mortality in SARS-CoV-2 stratified by hemoglobin levels: a retrospective study. *eJHaem*. 2021;2:335-339. doi:10.1002/jha2.195
12. Al-Jarallah M, Rajan R, Dashti R, et al. In-hospital mortality in SARS-CoV-2 stratified by serum 25-hydroxy-vitamin D levels: a retrospective study. *J Med Virol*. 2021;93:5880-5885. 10.1002/jmv.27133
13. Alroomi M, Rajan R, Omar AA, et al. Ferritin level: A predictor of severity and mortality in hospitalized COVID-19 patients. *Immun Inflamm Dis*. 2021;9:1648-1655. 10.1002/iid3.517
14. Laine T, Reyes EM. Tutorial: survival estimation for Cox regression models with time-varying coefficients using SAS and R. *J Stat Softw*. 2014;61:1-23.
15. Badr HS, Du H, Marshall M, Dong E, Squire MM, Gardner LM. Association between mobility patterns and COVID-19 transmission in the USA: a mathematical modelling study. *Lancet Infect Dis*. 2020;20(11):1247-1254. 10.1016/S1473-3099(20)30553-3
16. Asghar MS, Akram M, Rasheed U, et al. Derangements of Liver enzymes in Covid-19 positive patients of Pakistan: a retrospective comparative analysis with other populations. *Archives of Microbiology & Immunology*. 2020;4:110-120.
17. Daeppen JB, Smith TL, Schuckit MA. Influence of age and body mass index on gamma-glutamyltransferase activity: a 15-year follow-up evaluation in a community sample. *Alcohol Clin Exp Res*. 1998;22:941-944.
18. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. 2020;40(5):998-1004. 10.1111/liv.14435
19. Zhang J, Zhou L, Yang Y, Peng W, Wang W, Chen X. Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics. *Lancet Respir Med*. 2020;8:e11-e12.
20. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):25-434. 10.1016/S1473-3099(20)30086-4
21. Shao T, Tong Y, Lu S, et al. γ-Glutamyltransferase elevations are frequent in patients with COVID-19: a clinical epidemiologic study. *Hepatol Commun*. 2020;11;4(12):1744–1750. 10.1002/hep4.1576
22. Hashemi N, Viveiros K, Redd WD, et al. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: a multicentre United States experience. *Liver Int*. 2020;40(10):2515-2521. 10.1111/liv.14583

23. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;22(369):m1985. 10.1136/bmj.m1985

24. Iavarone M, D'Ambrosio R, Soria A, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol*. 2020;73:1063-1071.

25. Morgan K, Samuel K, Vandeputte M, Hayes PC, Plevris JN. SARS-CoV-2 Infection and the Liver. *Pathogens*. 2020;9(6):430. 10.3390/pathogens9060430

26. Tu W-J, Liu Q, Cao J-L, et al. γ-Glutamyl transferase as a risk factor for all-cause or cardiovascular disease mortality among 5912 ischemic strokes. *Stroke*. 2017;48(10):2888-2891.

27. Cao J, Tu W-J, Cheng W, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):748-755.