

## Impact of COVID status and blood group on complications in patients in hemorrhagic shock

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Received 7 September 2023

Accepted 23 February 2024

**ABSTRACT**

**Objective** Among critically injured patients of various blood groups, we sought to compare survival and complication rates between COVID-19-positive and COVID-19-negative cohorts.

**Background** SARS-CoV-2 infections have been shown to cause endothelial injury and dysfunctional coagulation. We hypothesized that, among patients with trauma in hemorrhagic shock, COVID-19-positive status would be associated with increased mortality and inpatient complications. As a secondary hypothesis, we suspected group O patients with COVID-19 would experience fewer complications than non-group O patients with COVID-19.

**Methods** We evaluated all trauma patients admitted 4/2020–7/2020. Patients 16 years or older were included if they presented in hemorrhagic shock and received emergency release blood products. Patients were dichotomized by COVID-19 testing and then divided by blood groups.

**Results** 3281 patients with trauma were evaluated, and 417 met criteria for analysis. Seven percent (29) of patients were COVID-19 positive; 388 were COVID-19 negative. COVID-19-positive patients experienced higher complication rates than the COVID-19-negative cohort, including acute kidney injury, pneumonia, sepsis, venous thromboembolism, and systemic inflammatory response syndrome. Univariate analysis by blood groups demonstrated that survival for COVID-19-positive group O patients was similar to that of COVID-19-negative patients (79 vs 78%). However, COVID-19-positive non-group O patients had a significantly lower survival (38%). Controlling for age, sex and Injury Severity Score, COVID-19-positive patients had a greater than 70% decreased odds of survival (OR 0.28, 95% CI 0.09 to 0.81;  $p=0.019$ ).

**Conclusions** COVID-19 status is associated with increased major complications and 70% decreased odds of survival in this group of patients with trauma. However, among patients with COVID-19, blood group O was associated with twofold increased survival over other blood groups. This survival rate was similar to that of patients without COVID-19.

**BACKGROUND**

COVID-19, caused by the SARS-CoV-2, has defined the modern pandemic, with over 600 000 attributable deaths in the USA alone thus far.<sup>1</sup> As research efforts developed to define, characterize, and mitigate the effects of COVID-19, patterns emerged in immunologic profiles of infected patients. One pattern, which seems to underpin the

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

⇒ A number of risk factors for mortality have been associated with COVID-19 infection.

**WHAT THIS STUDY ADDS**

⇒ In this retrospective observational cohort study, COVID-19-positive trauma patients in hemorrhagic shock were compared with similar patients without detectable COVID-19. The COVID-19 cohort experienced more complications and a 70% decreased odds of survival.

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The substantial increase in mortality associated with COVID-19 in cases of hemorrhagic shock should prompt early identification of infection and heightened awareness of its implications.

viral mechanism of systemic illness, is endothelial dysfunction.<sup>2</sup> Described early in the COVID-19 literature,<sup>3</sup> patients can develop a consumptive coagulopathy, resulting in both venous and arterial thromboembolic complications. The reported mechanisms include disruptions in von Willebrand factor, plasminogen activator inhibitor-1, syndecan-1, soluble thrombomodulin and a host of cytokine and complement pathways.<sup>4</sup>

These biochemical markers of endothelial injury have also been previously associated with the endotheliopathy of trauma. Dysfunctional coagulation associated with increased clot formation has long been a focus in the trauma community, as hemorrhagic shock and direct tissue trauma are known to damage the endothelium.<sup>5–9</sup> Early hypocoagulable states are followed by hypercoagulable complications among survivors.<sup>10–11</sup> The described pathways and markers of dysfunction appear to closely mimic COVID-19's coagulopathic profile.

In addition, evolving data suggest differences in outcomes following injury may differ among patient blood groups.<sup>12–13</sup> Following a similar pattern, several studies suggest blood group O may be associated with decreased SARS-Cov-2 infection rates and decreased severity of illness.<sup>14–19</sup> We sought to describe the outcomes of severely injured patients presenting with concomitant COVID-19 and examine potential links among blood groups. We hypothesized that, among injured patients presenting with hemorrhagic shock, COVID-19-positive status would be associated with increased mortality and inpatient complications compared

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**To cite:** Brill JB, Mueck KM, Cotton ME, et al. *Trauma Surg Acute Care Open* 2024;**9**:e001250.

with patients without COVID-19. Furthermore, we suspected blood group O would be protective compared with other blood groups in terms of mortality and those same complications.

## METHODS

### Study setting

The Institutional Review Boards of the University of Texas Health Science Center at Houston and the Memorial Hermann Hospital approved this study with a provision for waiver of informed consent as allowed under 45 CFR 46.116. The Red Duke Trauma Institute at Memorial Hermann Hospital is an American College of Surgeons verified level I trauma center and serves as the primary teaching hospital for the McGovern Medical School-University of Texas Health Science Center. The hospital has a 1058-bed capacity, located within the Texas Medical Center, and is home to the John S. Dunn Heliport, the busiest heliport in the USA for its size. Our trauma center has evaluated over 10 000 patients annually for the past 3 years, with an admission count exceeding 7000 patients annually. The most critically injured are cared for in a 23-bed shock-trauma intensive care unit (ICU).

### Study design and definitions

A prospectively collected database was developed to include information on all adult patients with traumatic mechanism presenting in hemorrhagic shock. All patients entered into the database April 1, 2020 through July 31, 2020 were then retrospectively evaluated. Specific inclusion criteria for the study were the following: patient age  $\geq 16$  years, traumatic mechanism of injury and transfusion of blood products on arrival due to systolic blood pressure (SBP)  $< 90$  mm Hg and/or arrival lactate  $> 4$  mg/dL. The start date represents the date at which standardized COVID-19 nucleic acid amplification testing (NAAT) was implemented for all admissions at Memorial Hermann Hospital, but before any population immunity or vaccinations would have occurred. The testing policy established at that time required in level I (highest-level) trauma activations: (1) a nurse-obtained nasopharyngeal swab at the time of arrival to the emergency department (ED) for non-intubated patients, or (2) a respiratory-therapist-obtained bronchoalveolar lavage for patients intubated before arrival at our facility. For patients proceeding directly to the operating room without ED evaluation, nasopharyngeal swab was performed in the operating room when feasible during the resuscitation. Patients not arriving as the highest-level trauma activation were tested in the ED as soon as admission orders were placed, although it should be noted that administration of blood products before or at our facility automatically meets level I activation criteria. Samples were analyzed at the in-house laboratory, and manufacturers of the diagnostic kits did not change during the study period.

*Hemorrhagic shock* was defined as reduced tissue perfused due to loss of blood volume, identified by arrival SBP  $< 90$  mm Hg and arrival lactate  $> 4$  mg/dL. Acute kidney injury (AKI) was defined as a rise in serum creatinine of threefold over baseline at admission, a rise in serum creatinine over 4 mg/dL, or need for dialysis not in the setting of pre-existing end-stage renal disease. *Pneumonia* diagnosis required entry in a clinical note in order to remove potential observation bias. Study personnel were prohibited from assigning this diagnosis in the database if clinical diagnosis had not been documented. Acute lung injury (ALI) was defined as persistent arterial partial pressure of oxygen to fraction of inspired oxygen ratio of  $< 300$  while intubated. Systemic inflammatory response syndrome (SIRS) required two or more

criteria of the following: temperature  $< 36$  or  $> 38^{\circ}\text{C}$ , pulse  $> 90$  bpm, respiratory rate  $> 20$  times/min, arterial partial pressure of carbon dioxide  $< 32$  mm Hg, leukocyte count  $< 4000$  or  $> 12\,000$  per  $\mu\text{L}$  or  $> 10\%$  band forms on differential. *Sepsis* was defined as SIRS in the presence of suspected or confirmed infection and was abstracted directly from clinical notes. Venous thromboembolism (VTE) was defined as any pulmonary embolism (PE) or deep vein thrombosis (DVT) diagnosed with any imaging modality, although CTA and extremity Duplex ultrasound were the diagnostic tests of choice throughout the study period. No screening protocol existed, and all orders for CTA were based on clinical suspicion. DVT was defined as thrombosis of a named deep vein of an extremity seen on knee-to-hip ultrasound documented by the attending radiologist's read. No routine screening studies for DVT were ordered. Thus, all studies were considered diagnostic, based on clinician suspicion prompting the study.

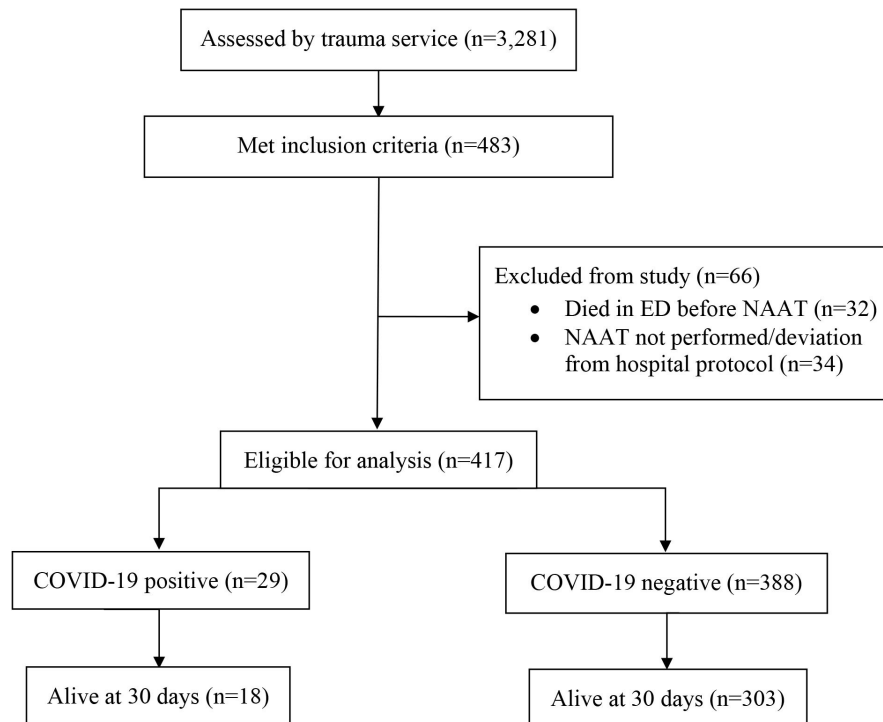
During the study period, all patients admitted to the trauma service after a level 1 activation was administered both mechanical and chemoprophylaxis for VTE. Guidelines stated that bilateral lower extremity sequential compression devices and early ambulation be started immediately after admission, excepting for injury patterns prohibitive of all mechanical prophylaxis applications. Chemoprophylaxis was also started on admission with either enoxaparin 30 mg subcutaneously every 12 hours or heparin 5000 units subcutaneously every 8 hours. An increase of 10 mg per dose of enoxaparin was ordered for patient weight over 90 kg. Solid organ injury delayed initiation of chemoprophylaxis by 24 hours. Intracranial hemorrhage delayed chemoprophylaxis for 24 hours after an interval CT-head showed no progression. Absolute contraindications such as active bleeding, hemodynamic instability and reported allergies also delayed chemoprophylaxis as clinically appropriate. The study was completed before ICU protocols were developed to start heparinoids at therapeutic dosing for COVID-19 patients with elevated inflammatory biomarkers.

Patients were included in the study analysis if they (1) were 16 years or older, (2) presented in hemorrhagic shock and (3) received emergency release blood products in the prehospital setting or the trauma bay. Patients bypassing the ED and proceeding directly to the operating room were also included if they met above criteria. Patients who died in the ED or prior to collecting NAAT samples were excluded. Patients were dichotomized into COVID-19 NAAT positive and COVID-19 not detected, hereafter referred to as 'negative'.

The primary outcome was 30-day survival. Secondary outcomes were clinically important complications, defined *a priori* as AKI, pneumonia, sepsis, VTE, ALI and SIRS. Relevant outcome measures were also examined, including hospital-free days, ICU-free days and ventilator-free days. Finally, patients were divided into group O and non-group O blood types. After analyzing all patients, we specifically evaluated only those who were COVID-19 positive.

### Statistical analysis

Continuous data are presented as medians with 25th and 75th IQR or as means with SD. Comparisons between groups were performed using the Wilcoxon rank sum (Mann-Whitney U test) or Student's t test, respectively. Categorical data are reported as proportions and, where appropriate, tested for significance using  $\chi^2$  or Fisher's exact tests. Multivariate logistic regression model then evaluated survival. Purposeful regression modeling was used to construct a multivariate logistic regression model using the technique of purposeful selection of covariates described



**Figure 1** CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; ED, emergency department; NAAT, nucleic acid amplification testing.

by Hosmer and Lemeshow.<sup>20</sup> This modeling process allows for inclusion of the analyst in the variable selection decision, ensuring clinically relevant variables are included in the final ‘best fit’ model. Clinically sound and independent variables were chosen from univariate analysis, including age, sex, mechanism of injury, injury severity (both ISS and AIS), vital signs and arrival laboratory values. These variables were entered into stepwise regression that selected three variables of significance (age, sex and ISS in the first model and prehospital blood pressure and ISS in the second). These were then applied to a multivariate logistic regression analysis evaluating the variables impact on the dependent variable, 30-day survival. In the first model, COVID-19 status was added to this purposeful model, while blood group O was added as an independent variable. Data were analyzed using STATA Statistical software (V.12.1; College Station, Texas).

## RESULTS

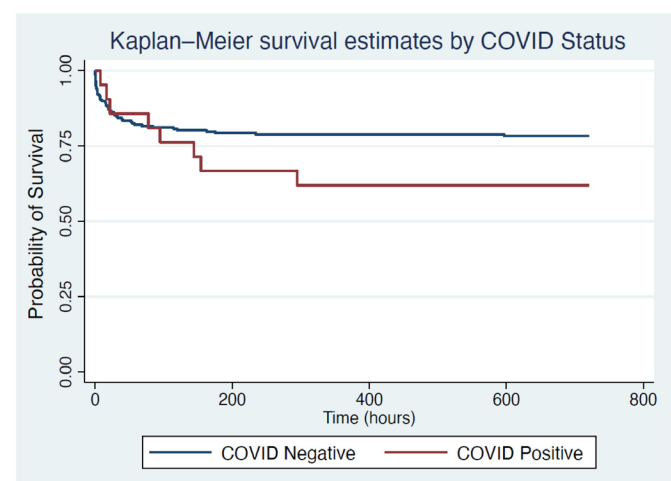
During the study period, 3281 patients were evaluated by the trauma service. Of these, 483 met inclusion criteria. Thirty-two patients died in the ED before NAAT was performed, with a further 34 patients who did not received NAAT on admission to the hospital. Half of these protocol violations (n=17) occurred in the first 30 days of the NAAT policy creation. Twenty-nine (7%) analyzed patients were COVID-19 positive, of whom 13 (59%) were symptomatic on admission or during their hospital stay. The remaining 388 (93%) were COVID-19 negative. Eighteen of the 29 COVID-19-positive patients (64%) survived to 30 days after admission, compared with 303 of 388 COVID-19-negative patients (78%) surviving (figure 1)(figure 2).

### COVID status

There were no differences in baseline demographics between the COVID-19-positive and negative groups (table 1). In addition, mechanism of injury, AIS and ISS were similar. With the exception of scene systolic pressure (median 113 (92, 139) vs 99 (74,

127),  $p=0.010$ ), scene vital signs were similar between groups. Both groups arrived with similar vital signs and had similar initial laboratory values (table 2). Positive ED-focused assessment for the sonography of trauma examinations was similar (25% in COVID-19-positive and 30% in COVID-19-negative patients), as were massive transfusion protocol activations (43 and 48%, respectively). There were no differences in ED or post-ED blood transfusions.

Patients who were COVID-19 positive experienced higher complication rates than the COVID-19-negative cohort (table 3). AKI, pneumonia, sepsis, VTE and SIRS all appeared more frequently in the COVID-19 cohort. While hospital-free and ventilator-free days were not statistically different, ICU-free days were less in those who were COVID-19 positive. While a large absolute difference existed between the groups in 30-day



**Figure 2** Kaplan-Meier survival curve.

**Table 1** Patient demographics and baseline data

	COVID-19 positive n=29 (IQR)	COVID-19 negative n=388 (IQR)	P value
Median age, years	34 (22, 43)	33 (21, 51)	0.676
Male sex	76%	74%	0.812
White race	42%	33%	0.322
BMI	27.4 (24.4, 30.6)	25.6 (22.4, 31.3)	0.306
Penetrating mechanism	43%	32%	0.223
Median head AIS	4 (2, 5)	3 (2, 5)	0.701
Median chest AIS	3 (2, 3)	3 (2, 3)	0.728
Median abdomen AIS	3 (0, 4)	3 (0, 4)	0.743
Median extremity AIS	3 (2, 3)	3 (2, 3)	0.544
Median ISS	26 (14, 34)	26 (17, 38)	0.616

AIS, Abbreviated Injury Scale; BMI, body mass index; ISS, Injury Severity Score.

survival (62 vs 78%), this did not reach statistical significance ( $p>0.05$ ). No patients receiving emergency release blood products experienced transfusion-related ALI, transfusion associated cardiac overload or any other clinically significant transfusion reaction as defined by hospital blood bank protocol.

In multiple logistic regression modeling, controlling for age, sex and ISS, COVID-19-positive patients had a greater than 70% decreased odds of survival compared with their COVID-19-negative cohorts (OR 0.28, 95% CI 0.09 to 0.81;  $p=0.019$ ).

### Impact of blood group on outcomes

Of the 417 patients, 219 were blood group O and 198 were non-group O (ie, group A, B or AB). There were no differences in demographics, mechanism of injury or injury severity (table 4). With the exception of scene SBP being higher in group O (median 110 mm Hg vs 97,  $p=0.025$ ), there were no differences in scene vital sign, nor in resuscitation

**Table 2** Arrival physiology, laboratory values and transfusion data

	COVID-19 positive n=29 (IQR)	COVID-19 negative n=388 (IQR)	P value
Median arrival HR	109 (94, 140)	104 (85, 124)	0.310
Median arrival SBP	110 (80, 122)	108 (90, 124)	0.829
Median arrival GCS	6 (3, 15)	13 (3, 15)	0.552
Median arrival hemoglobin	12.6 (11.7, 13.5)	12.4 (11.1, 13.9)	0.784
Median arrival platelet count	189 (154, 242)	217 (163, 265)	0.449
Median arrival base excess	-4 (-9 to -2)	-4 (-8 to -2)	0.946
Median arrival lactate	5.0 (4.0, 7.3)	4.5 (2.8, 6.7)	0.134
Median arrival rTEG ACT	113 (105, 128)	105 (101, 121)	0.095
Median arrival rTEG angle	71 (63, 74)	72 (66, 76)	0.372
Median arrival rTEG MA	62 (43, 66)	62 (56, 66)	0.436
Median arrival rTEG LY30	0.7 (0.0, 7.1)	0.7 (0.0, 2.3)	0.363
Mean ED RBC, U	1 (0, 3)	1 (0, 3)	0.789
Mean ED plasma, U	1 (0, 4)	1 (0, 3)	0.839
Mean ED platelets, U	0 (0, 0)	0 (0, 0)	0.735
Mean ED whole blood, U	0 (0, 1)	0 (0, 1)	0.944
Mean post-ED RBC, U	2 (1, 4)	2 (0, 6)	0.910
Mean post-ED plasma, U	2 (1, 5)	2 (0, 6)	0.962
Mean post-ED platelets, U	0 (0, 1)	0 (0, 1)	0.948

ACT, activated clotting time; ED, emergency department; GCS, Glasgow Coma Scale; HR, heart rate; LY30, percent lysis at 30 min; MA, maximum amplitude; RBC, packed red blood cells; rTEG, rapid thrombelastography; SBP, systolic blood pressure; U, unit.

**Table 3** Complications and outcomes

	COVID-19 positive (n=29)	COVID-19 negative (n=388)	P value
Acute kidney injury	30%	12%	0.006
Pneumonia	43%	13%	<0.001
Sepsis	43%	20%	0.004
Venous thromboembolism	33%	14%	0.006
Acute respiratory distress syndrome	22%	13%	0.173
SIRS	81%	58%	0.014
Hospital-free days	5 (0, 15)	12 (0, 22)	0.115
ICU-free days	5 (0, 25)	25 (0, 29)	0.017
Ventilator-free days	21 (0, 30)	28 (2, 30)	0.109
30-day survival	18 (62%)	303 (78%)	0.083

ICU, intensive care unit; SIRS, systemic inflammation response syndrome.

requirements. As well, arrival vitals and labs were similar except for coagulation parameters by rapid thrombelastography (rTEG), where blood group O patients were less coagulopathic (table 5). With respect to complications, there were no differences in AKI, sepsis or VTE. There was, however, a higher incidence of ALI in the group O blood patients. There were no differences in hospital, ICU or ventilator-free days. There was also no difference in 30-day survival by blood group (80 vs 76%,  $p=0.325$ ) (table 6).

### Impact of blood group on outcomes in COVID(+) patients

Among the 29 COVID-19-positive patients, 19 were group O, and 10 were non-group O. There were no differences in demographics between the two groups. However, the incidence of penetrating mechanism was higher and, as a result, the ISS was lower among group O patients (table 4). Scene vital signs, with the exception of higher scene SBP among group O patients (median 108 (101, 124) vs 88 (79, 96);  $p=0.045$ ), were similar, as were prehospital resuscitation volumes. Arrival vitals and

**Table 4** Patient demographics and baseline data by blood group

All patients			
	Group O blood (n=219) (IQR)	Non-group O blood (n=198) (IQR)	P value
Median age, years	36 (27, 54)	37 (23, 54)	0.804
Male sex	70%	74%	0.334
White race	37%	38%	0.855
BMI	26.8 (22.4, 30.6)	25.6 (22.4, 31.3)	0.306
Penetrating mechanism	43%	31%	0.180
Median ISS	27 (14, 38)	26 (17, 38)	0.743
COVID-19-positive patients only			
	Group O blood (n=19)	Non-group O blood (n=10)	P value
Median age, years	32 (22, 36)	37 (20, 49)	0.663
Male sex	77%	80%	0.909
White race	30%	20%	0.341
BMI	27.7 (24.4, 32.8)	27.1 (24.1, 29.9)	0.717
Penetrating mechanism	54%	30%	<0.001
Median ISS	18 (10, 26)	28 (18, 32)	0.031

BMI, body mass index; ISS, Injury Severity Score.



**Table 5** Arrival physiology, laboratory values and transfusion data by blood group

All patients			
	Group O blood type (n=219)	Non-group O blood (n=198)	P value
Median arrival HR	109 (85, 129)	100 (86, 122)	0.296
Median arrival SBP	101 (86, 123)	110 (91, 130)	0.113
Median arrival GCS	8 (3, 15)	13 (3, 15)	0.289
Median arrival rTEG ACT	105 (97, 121)	113 (105, 128)	0.085
Median arrival rTEG angle	73 (67, 76)	71 (64, 75)	0.081
Median arrival rTEG MA	63 (58, 63)	60 (54, 65)	0.031
Mean ED blood products, U	1 (0, 3)	1 (0, 3)	0.789
Mean post-ED blood products, U	2 (1, 5)	2 (0, 6)	0.962
COVID-19-positive patients only			
	Group O blood (n=19)	Non-group O blood (n=10)	P value
Median arrival HR	118 (98, 130)	100 (86, 108)	0.103
Median arrival SBP	105 (90, 127)	121 (110, 140)	0.346
Median arrival GCS	13 (3, 15)	13 (3, 11)	0.490
Median arrival rTEG ACT	113 (105, 128)	113 (105, 128)	0.832
Median arrival rTEG angle	73 (69, 74)	68 (58, 73)	0.278
Median arrival rTEG MA	63 (56, 67)	58 (49, 65)	0.310
Mean ED blood products, U	3 (1, 9)	4 (3, 6)	0.609
Mean post-ED blood products, U	1 (0, 7)	5 (0, 9)	0.622

ACT, activated clotting time; ED, emergency department; GCS, Glasgow Coma Scale; HR, heart rate; MA, maximum amplitude; rTEG, rapid thrombelastography; SBP, systolic blood pressure; U, units.

**Table 6** Outcomes based on blood group and COVID-19 status

All patients			
	Group O blood type (n=219)	Non-group O blood (n=198)	P value
Acute kidney injury	12%	17%	0.324
Sepsis	22%	23%	0.906
Venous thromboembolism	16%	12%	0.186
Acute respiratory distress syndrome	19%	11%	0.010
Hospital-free days	12 (0, 21)	9 (0, 22)	0.980
ICU-free days	25 (0, 30)	23 (0, 28)	0.591
Ventilator-free days	28 (2, 30)	27 (0, 30)	0.525
In-hospital survival	80%	76%	0.326
COVID (+) patients only			
	Group O blood (n=19)	Non-group O blood (n=10)	P value
Acute kidney injury	15%	40%	<0.001
Sepsis	38%	50%	0.533
Venous thromboembolism	23%	50%	0.139
Acute respiratory distress syndrome	15%	20%	0.509
Hospital-free days	13 (0, 23)	0 (0, 3)	0.043
ICU-free days	22 (0, 29)	0 (0, 3)	0.027
Ventilator-free days	28 (0, 30)	0 (0, 15)	0.053
In-hospital survival	79%	40%	0.028

ICU, intensive care unit.

laboratory values were similar between group O and non-group O patients, as were resuscitation products and volumes (table 5). Length of stay and complications were lower and 30-day survival significantly higher in group O patients (table 6). In fact, survival for COVID-19-positive blood group O patients was similar to that of COVID-19-negative patients (79 vs 78%).

In multiple logistic regression modeling, controlling for prehospital SBP and ISS, blood group O COVID-19-positive patients carried a twofold higher likelihood of survival (OR 2.11, 95% CI 1.02 to 4.35; p=0.043) when compared with their non-group O counterparts.

## DISCUSSION

In this retrospective observational cohort study, COVID-19-positive status was associated with a decrease in likelihood of survival in patients arriving in hemorrhagic shock. These patients also experience a nearly twofold increased risk of major complications, including AKI, pneumonia, sepsis, VTE and SIRS. We were able to accept our hypothesis that, compared with hemorrhagic shock patients in whom COVID-19 is not detected, COVID-19 is associated with increased mortality and inpatient complications.

This finding corroborates a recent multicenter retrospective study matching 53 COVID-19-positive trauma patients to 106 patients without COVID-19.<sup>21</sup> Yeates *et al* found that patients with detectable COVID-19 had increased mortality (9.4% vs 1.9%, p=0.029), pneumonia (7.5% vs 0.0%, p=0.011) and longer lengths of stay (7.47 vs 3.28 days, p<0.001). Similarly, a retrospective study of 4912 hospitalized trauma patients at Grady Memorial Hospital found a higher complication rate in their COVID-19-positive patients. The COVID-19 cohort had higher rates of AKI, sepsis, unplanned intubations and return to the ICU.<sup>22</sup> Survival showed no difference, however. One key difference of this study was its more general trauma population with median ISS 11.9–13.5 compared with our patients in hemorrhagic shock (ISS 26). In other retrospective analyses, Klutts *et al*<sup>23</sup> and Kaufman *et al*<sup>24</sup> found longer lengths of stay in their COVID-19-positive trauma patients. This finding also correlates with our clinical experience early in the pandemic, when critically injured patients would appear to survive their initial episode of shock, to then experience multiple complications and sometimes multiorgan failure days to weeks later. This ‘third wave’ of mortality was previously part of the dreaded trimodal distribution of death after trauma. More recently, modern trauma systems with improved access to care and resuscitation strategies appeared to eliminate this late peak.<sup>25 26</sup> To avoid a return of late ICU-stage mortality, at least in COVID-19 cases, requires a complex response that lies outside the purview of this study.

As with early reports in non-trauma patients with COVID-19,<sup>16 27–29</sup> blood group O was associated in our study with a twofold increased survival among trauma patients presenting in hemorrhagic shock. How this association exists, and what therapeutic implications it may have, are areas of intense research activity. Interestingly, this finding of group O as protective for COVID-19 directly opposes a recently reported association of group O in trauma. A retrospective study followed by a prospective multicenter study<sup>12 13</sup> found an association between group O and increased mortality after severe trauma. These studies’ findings directly conflict with other reports finding no difference in mortality between group O versus other blood groups,<sup>30–32</sup> making it difficult to draw any conclusions regarding blood group effects on trauma outcomes at this time.

While a molecular description of the pathways underlying COVID and hemorrhagic shock was well beyond the design of this study, similarities seem to exist. Severe trauma, accompanied by hemorrhagic shock, produces systemic breakdown of the endothelial glycocalyx on the endoluminal surface of blood vessels.<sup>33–35</sup> The glycocalyx, during early SARS-CoV-2 infection, suffers degradation through several inflammation pathways.<sup>36–38</sup> Normally, the glycocalyx allows for interaction with intraluminal cells and large molecules while maintaining a barrier to whole cells and inhibiting platelet adhesion within the microvasculature.<sup>8 36 39</sup> As COVID-19 progresses, however, glycocalyx disruption promotes microthrombosis, particularly within the pulmonary vasculature.<sup>40</sup> Injury to the endothelial glycocalyx leads to interstitial edema, inflammation and tissue hypoxia.<sup>41 42</sup> We are certainly not the only surgeons to note the biochemical similarities, however, and these similarities may open doors for intervention by way of proven trauma resuscitation strategies.<sup>43</sup>

While the study benefits from a robust, prospectively designed database tracking patients in hemorrhagic shock, its limitations are numerous. Overall power of the study is low given the short time span and small number of COVID-19-positive patients. As a single-center retrospective study, performed early in the COVID-19 pandemic, its results may not be generalizable. New variants continue to emerge, some with significantly different transmissibility and effects within the population.<sup>44–46</sup> Vaccines were undergoing clinical trials at the time, so results in vaccinated individuals were unavailable for this study. The time frame of the study was chosen specifically to limit confounders such as vaccination status, but then the results may not apply to patients previously recovered from COVID-19 infection or those with multiple rounds of vaccination. Further study is ongoing to establish external validity of our findings. Not all patients were symptomatic despite positive NAAT. This may be partly explained by the difficulty in elucidating symptoms, or any history for that matter, from an unstable patient in hemorrhagic shock. No meaningful comparisons between symptomatic versus asymptomatic patients could be made. Selection bias is possible, given that some complication data (sepsis, pneumonia) were abstracted from notes, and the treatment team was reminded of patients' COVID-19 status every time they entered the room in full personal protective equipment. Biochemical markers were not included in the study, which was designed in February 2020, just as early literature was being published regarding what biomarkers were potentially important in COVID-19 infection. Finally, 20% of the patients meeting inclusion criteria did not have NAAT results. While the 32 patients who died in the ED by definition could not have affected the secondary outcomes of complications, this part of the patient population directly affects the primary outcome of 30-day survival, raising the question of survival bias. The decision to exclude early deaths, however, focuses the study on the effects of COVID-19 on those patients who survive the initial traumatic insult.

The substantial increase in mortality associated with COVID-19 in cases of hemorrhagic shock should prompt early identification of infection and awareness of multiple complications associated with COVID-19 infection. Further research efforts are warranted to elucidate the pathologic mechanisms at play, in the hopes of identifying potential targets of intervention.

**Contributors** JBB and BAC designed this study. JBB, KMM, MEC, BT, MS, LSK and BAC collected and analyzed the data. JBB, KMM, MEC, BT, MS, LSK and BAC participated in data interpretation and manuscript preparation. JBB is the author responsible for overall content as the guarantor. The views expressed in this manuscript reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense nor the US Government.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by University of Texas Health Science Center at Houston and Memorial Hermann Hospital; HSC-MS-18-0258. The Institutional Review Boards of the University of Texas Health Science Center at Houston and the Memorial Hermann Hospital approved this study with a provision for waiver of informed consent as allowed under 45 CFR 46.116.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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