Fluid Overload is Associated with Poor Prognosis in Hospitalized Patients with Covid-19 and Acute Kidney Injury

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Abstract

Introduction:

Acute kidney injury (AKI) has been associated with adverse outcomes among hospitalized patients with Covid-19. Although pre-pandemic data of patients with AKI has shown that volume overload is significantly associated with mortality and need for Renal Replacement Therapy (RRT), the association with worst outcomes among patients with AKI and Covid-19 has not been studied. Thus, the purpose of the study was to evaluate the effect of fluid overload in AKI with progression of the disease and mortality among patients hospitalized with Covid-19.

Methods

Observational retrospective cohort study that included volume balances, clinical and biochemical data of 412 hospitalized patients with Covid-19 and AKI. Univariate and Cox regression analyses were used to evaluate the association of fluid overload with 28-day mortality, AKI stage 3 and RRT.

Results

The mean age of the subjects was 55 ± 15 years, 64.1% were women, 69.7% developed AKI at any stage, 47.2% had diabetes, 31.4% had hypertension, and only 4.5% had chronic kidney disease. Likewise, the 28-day mortality was 20.4%, 43.3% patients required mechanical ventilation, 22.3% developed AKI stage 3, and 9.5% needed RRT. The median of global fluid overload was 1441 cc (-489 to 3736), and 59.7% had a global fluid overload of > 1000 cc at discharge. After Cox regression analysis the risk for 28-day mortality, AKI stage 3 and RRT was HR = 3.014 (1.573–5.777), 3.159 (1.708–5.840), and 3.607 (1.128–11.539), respectively (p < 0.05 for all).

Conclusion

In the setting of AKI, fluid volume overload was associated with worst outcomes among hospitalized patients with Covid-19.

Introduction

Over the last two years, the pandemic of Covid-19 has represented the leading cause of morbimortality around the world, and Acute Kidney Injury (AKI) has been associated with greater risk of complications, and direr outcomes among hospitalized patients with severe Covid-19 infection. Some of the factors associated with poor prognosis in patients with AKI and Covid-19 were older age, uncontrolled comorbidities, and mechanical ventilation, among others. Nevertheless, since most of these factors are
not modifiable during hospitalization, yielding novel therapeutic options among this group of patients are needed.

Previous data have shown that Covid-19 can induce AKI by heterogenous mechanisms\textsuperscript{4,5}. In fact, the viral-induced-kidney damage can lead to acute tubular necrosis, collapsing glomerulopathy and mitochondrial impairment\textsuperscript{5}. Thus, patients with AKI at any stage who survive have reduced renal function and an increased risk for requiring dialysis at any point after discharge\textsuperscript{6,7}.

Fluid therapy is a common management centered on restoring hemodynamic stability and maintaining vital organs perfusion\textsuperscript{8,9}. Pre-pandemic data of patients with AKI has shown that volume overload is significantly associated with more respiratory failure, need for mechanical ventilation, sepsis, and other adverse outcomes\textsuperscript{8–11}. Despite fluid overload leads to several complications, the role of intravenous fluid management in patients hospitalized for Covid-19 with AKI has not been fully studied. Thus, the aim of the present work was to evaluate whether fluid overload could be associated with increased mortality and worst outcomes in hospitalized patients with severe Covid-19 and AKI.

**Material And Methods**

**Subjects**

This was a retrospective observational study that selected patients from the records of the Internal Medicine department of the Hospital General Dr. Manuel Gea Gonzalez (HGDMGG) that received attention from April 2020 to December 2021. Patients aged > 18 years old with confirm Covid-19 infection by positive polymerase chain reaction testing of a nasopharyngeal sample for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who were admitted were eligible for the study. Severe Covid-19 infection was defined as clinical signs of dyspnea, respiratory frequency over 30/min, oxygen saturation less than 93%, arterial oxygen partial pressure/ fractional inspired oxygen (PaO2/FiO2) ratio less than 300 and/or lung infiltrates more than 50% of the lung field within 24–48 hours\textsuperscript{12}. Likewise, AKI was defined according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria as follows: stage 1, as an increase in serum creatinine level by 0.3 mg/dL within 48 hours or 1.5 to 1.9 times increase in serum creatinine level from baseline within 7 days; stage 2, as 2 to 2.9 times increase in serum creatinine level within 7 days; and stage 3, as 3 or more times increase in serum creatinine level within 7 days or initiation of dialysis\textsuperscript{3}. Overall, records from 1057 hospitalized patients were analyzed. Of them, 586 patients were excluded due to incomplete clinical and biochemical data. Furthermore, 59 patients who did not have a complete fluid balance during the whole hospitalization were excluded from the final analysis. The present study was approved by the HGDMGG Human Biomedical Research Institutional Committee (REF 97/22) and written informed consent was waived given the retrospective nature of the study.

Clinical and biochemical data were obtained at admission. Fluid volume status was assessed using the balance of the input and output of fluids in the body and the global fluid overload was estimated as the sum of every 24-hours fluid balance during the hospital stay\textsuperscript{11}. Afterwards, global fluid overload was
categorized into quartiles as: -489 cc, -490 to 1440 cc, 1441 to 3735 cc, and > 3736 cc. The Body Mass Index (BMI) was calculated as the basal weight in kilograms (kg) divided by the square of body height in meters (m$^2$); normal weight was defined as < 25 kg/m$^2$, overweight as BMI between 25-29.9 kg/m$^2$, and obesity as BMI $\geq$ 30 kg/m$^2$. Hypertension was defined as BP values $>$ 140/90 mmHg or prior documented diagnosis. Type 2 diabetes was defined when fasting plasma glucose values were $\geq$ 126 mg/dL or when the patient self-reported a previous diagnosis or current hypoglycemic drug use. Chronic kidney disease (CKD) was defined by the KIDGO guidelines as a glomerular filtration rate $<$ 60 ml/min/1.73m$^2$ for more than 3 months, structural renal changes, or when the patient self-reported a previous diagnosis.

**Biochemical analysis**

The central laboratory of the HGDMGG performed all biochemical laboratory measurements. Blood samples from the patients were collected after at admission to the emergency department. The measurements were carried out with commercially available standardized methods. Serum creatinine, blood nitrogen urea (BUN), C-reactive protein (C-RP), and lactic dehydrogenase (LDH), were measured using DxC 700 AU Chemistry Analyzer (Beckman Coulter, Fullerton CA). Plasma ferritin concentrations were estimated using enzyme-linked immunosorbent assay (Beckman Coulter DxC 600i, Fullerton CA). D Dimer levels were estimated using an ACL Top 550 CTS (Werfen Company, Spain).

**Outcomes**

The primary outcome was 28-day mortality according to global fluid overload. In addition, progression to AKI stage 3, and the need for in-hospital dialysis (hemodialysis or peritoneal dialysis) were considered as secondary outcomes.

**Statistical Analysis**

Values are expressed as mean ± standard deviation, median (interquartile range) or frequencies (%). Means and medians were compared using ANOVA or Kruskal-Wallis tests (Mann-Whitney’s U test for individual comparison between groups) when needed, and frequencies with chi-squared test. The survival rate curves according to the number of AKI stages and the nominal global fluid overload were plotted via the Kaplan-Meier method with the statistical significance examined by the log rank test. Multivariate Cox regression analysis was performed and hazard ratios (HRs) with 95% confidence intervals (95%CI) were estimated to evaluate the effect of baseline variables with 28-day mortality, progression to AKI stage 3, and renal replacement therapy (RRT). All variables significantly associated with mortality, as well as those with biological plausibility or scientific evidence, were included in the multivariate model. Analyzes were performed using the SPSS v. 25.0 statistical package (SPSS Chicago, Il.). All values with $p < 0.05$ or 95% confidence intervals (95% CI) that excluded the unit, were considered statistically significant.

**Results**
The study included 412 hospitalized patients with severe Covid-19 infection, of them, 69.7% (n= 287) patients developed AKI at any stage, and had a median hospital stay of 10 days (6-17). The mean age of the subjects was 55.2 ± 14.8 years, 64.1% (n= 264) were women, had a mean BMI of 38.2 ± 5.5 kg/m² (29.6% had normal weight, 38.5% had overweight and 31.8% had obesity), 47.2% had type 2 diabetes, 31.4% had hypertension, and only 4.5% had CKD. Of note, only less than 20% (n= 78) of patients received at least one dose of SARS-CoV-2 vaccine. Likewise, the 28-day mortality was 20.4% (n=84), 43.3% patients required mechanical ventilation (n=93), and 9.5% needed RRT (n= 31) [8.5% (n=28) and 1.5% (n= 5) received hemodialysis or peritoneal dialysis, respectively]. As seen in figure 1, the rate of mortality, mechanical ventilation and RRT increased as the severity of AKI progressed (p<0.001 for all). The median of global uid balance was 1441 cc (-489 to 3736), and 59.7% had a global overload of >1000 cc at hospital discharge.

Clinical and biochemical characteristics of the subjects classified by AKI stages are shown in table 1. Compared with patients without AKI, those with any AKI stage were significantly older, more likely to be women, had lower BMI, had more patients with obesity, lower prevalence of hypertension, higher frequency of CKD, and as the severity of AKI progressed, levels of D-dimer, BUN, LDH, C-RP, and ferritin were higher (p<0.05 for all). Only patients without AKI had significantly higher global fluid overload than AKI stage 1 (p<0.001). However, patients with AKI stage 3 had the highest prevalence of at 4th quartile of global fluid overload (figure 2). Patients at the lowest global fluid overload quartile had lower D-Dimer, LDH, C-RP and ferritin levels (p<0.001) and tended to have lower need for RRT than the other three quartiles, but it was not statistically significant (4.3% vs 9.0% vs 14.1 vs 11.5% for 1st, 2nd, 3rd, and 4th fluid overload quartiles, respectively; p= 0.148). On the other hand, patients at 4th fluid overload quartile had longer hospital stay than the other groups (9 [6-17] vs 9.5 [6-16] vs 9 [6-14] vs 11 [7-18] days for 1st, 2nd, 3rd, and 4th fluid overload quartiles, respectively, p<0.001). Figure 3 shows the Kaplan-Meier plots for 28-day mortality according to global fluid overload quartiles, and for categorical >1000 cc global volume overload. Only 8.7% (n= 9) patients died in the 1st quartile, whereas 20.6% (n= 21), 22.1% (n= 23), and 30.1% (n= 31) died in the rest 2nd, 3rd, and 4th quartiles, respectively; p<0.001).

Multivariate Cox regression analyses were used to predict 28-day mortality, progression to AKI stage 3, and RRT (Table 2). Model 1 was adjusted by age, sex, and BMI; model 2 included model 1 plus adjustment by type 2 diabetes, hypertension, CKD, mechanical ventilation, and vasopressor use; and model 3 included model 2 plus biochemical inflammatory markers such as D-Dimer, LDH, C-RP, and ferritin. When the patients who survived were used as reference, a global fluid overload >1000 cc was unadjusted and independently associated with higher 28-day mortality risk. Of note, the inclusion of comorbidities increased the risk for mortality by 71.9%, but the addition of inflammatory markers did not modify the associations seen. Along with these results, a global fluid overload >1000 cc showed stronger independent risk for AKI 3 progression and need for dialysis than mortality itself. As a matter of fact, the inclusion of comorbidities increased the risk by 52.3% and 112.8%, for AKI stage 3 and RRT, respectively. And, when the inflammatory markers were added, the risk increased by 59.3% and 1.6% for AKI 3 and need for dialysis, respectively.
**Discussion**

Acute Kidney Injury is one of the most common complications of Covid-19 and it has been associated with increased risk of death, prolonged stay in hospital, and need for RRT. Although age, male sex, and previous uncontrolled comorbidities, such as cardiovascular disease, diabetes and CKD, have been independently associated with worst outcomes among patients with Covid-19 and AKI, few of them are relatively modifiable during hospitalization that could improve prognosis. Likewise, data from previous studies have only focused on clinical and biochemical characteristics and have not widely analyzed patient’s volume status in non-acute heart failure context and/or previously treated with RRT. Since volume overload, as main determinant of starting dialysis therapy, has been associated with increased mortality in non-Covid-19 patients, the aim of the present study was to determine whether fluid overload during whole hospitalization could be associated with worst outcomes in these patients. From this retrospective observational study, the global fluid overload, known as the cumulative sum of inputs/outputs of patient’s fluid balances, was independently associated with more than three-fold higher risk for 28-day mortality, AKI stage 3 and need for dialysis therapy among hospitalized patients with Covid-19 and AKI. To the best of our knowledge, this is the first study to demonstrate that achieving more neutral fluid volume balances at discharge reduce significantly morbimortality among these patients.

Volume overload is a frequent complication in critically ill patients with AKI, with a high incidence ranging from 30–70%. Most of this pre-pandemic data comes from Intensive Care Units (ICU) populations with sepsis and shock, where fluid resuscitation would be more intensive. In fact, a meta-analysis of 12 cohort studies including patients with AKI found that categoric volume overload was associated with mortality (OR = 2.23 [1.66–3.01]; I² = 62%). Nevertheless, results from this meta-analysis should be taken with caution since definition of fluid overload was remarkably heterogenous and most of observational studies use an arbitrary definition of percentage of gain from basal weight. In the present study, a 5–10% and > 10% of body weight at admission was independently associated with increasing risk of dead (HR = 3.120 [1.411–6.896] and 2.792 [1.254–6.213], respectively; data not shown). However, knowing that weight may change (gain or loss) during hospitalization, and acknowledging that patients were only weighed at admission, this data was not included in the final analysis. Nonetheless, compared with results reported by Fülöp et al, Bouchard et al, and Heugh et al, the association with increased mortality in our study was higher.

Progression and longer duration of AKI in patients with Covid-19 was widely reported in different centers worldwide. Likewise, severity of respiratory failure, multiorgan involvement, mechanical ventilation, and ICU admission were consistent findings among patients who progressed to AKI stage 3. Although few studies reported fluid balances of patients with AKI and Covid-19 during hospitalization, none of them found an association of fluid overload and worst outcomes. In the present study, patients with AKI stage 3 had significantly higher positive fluid balances, and less than one third had a global balance < 1000 cc. Since SARS-CoV-2-induced AKI can be multifactorial, it is possible that those patients who first developed intrinsic AKI (by oliguric acute tubular necrosis rather than...
prerenal AKI by dehydration and hypotension) could have had higher odds for AKI stage 3 when they were subjected with increased volume loads at admission.\textsuperscript{4,5} Although viremia and direct impact of the virus have been reported on the renal tubules, scarce information is available to identify an independent association of fluid overload and SARS-CoV-2-direct damage to the kidney.

AKI represents a marker of Covid-19 severity, and nearly one third would need RRT.\textsuperscript{15,19} In the present study, 54.8% of patients receiving RRT died and had significantly higher fluid overload. In line with these results, data from the STOP-COVID study showed that among patients with RRT, 63% died during hospitalization, and among those who survived, 34% remained dependent to dialysis on discharge.\textsuperscript{6} Patients with AKI and Covid-19 who were dependent to dialysis were more likely to be older and have CKD, suggesting that reserve renal function was lower in these patients.\textsuperscript{6} This could partially explain why the addition of variables associated with reduced baseline renal function into the multivariable model increased the risk for needing RRT during hospitalization.

The present study has several strengths. To the best of our knowledge, this was the first study to describe the significant and independent association of volume overload with worst outcomes in severe Covid-19 and AKI. Another strength is that the population included were exclusively patients with severe Covid-19, which allowed us to analyze the course of the disease in the setting of severe inflammation. On the other hand, our study has some important limitations. As a single-center retrospective study in Mexico, the results may be difficult to generalize, and further studies are needed to confirm our findings. Second, only the weight at admission was reported, and changes of weight during hospitalization that could be useful to correctly define percentage of weight gain were not measured. Third, we did not determine the etiology of the AKI, nor the prerenal or intrinsic source of the injury. Fourth we do not report post discharge data of the patients, thus the effect of volume overload moths after discharge remains unknown.

In conclusion, in this retrospective cohort study of hospitalized patients with AKI and severe Covid-19, global fluid overload was associated with higher risk of 28-day mortality, progression to AKI stage 3, and need for RRT, independently of inflammatory markers and clinical cofounders. The magnitude of the associations presented here may promote more strict fluid de-resuscitation decisions and more directed conservative fluid management strategy in patients with Covid-19.

Declarations

Disclosure

The authors have nothing to disclose.

Acknowledgements

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Author contributions

H.R.G.S, F.D.M.S. and J.B.J. conceived the project, researched and analyzed data, contributed to discussion, and wrote the manuscript. J.L.T.C., L.I.S., A.D.J., V.P.V.A., S.S.A., M.A.S.R. and E.K.T.A. researched data and contributed with discussion. F.D.M.S. and J.B.J. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References


Tables

Table 1. Clinical and biochemical characteristics of subjects hospitalized with Covid-19 and Acute Kidney Injury
<table>
<thead>
<tr>
<th>Variables</th>
<th>Without AKI (n= 125)</th>
<th>KDIGO 1 (n= 139)</th>
<th>KDIGO 2 (n= 56)</th>
<th>KDIGO 3 (n= 92)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.7 ± 8.4</td>
<td>55.6 ± 14.6</td>
<td>50.8 ± 8.0</td>
<td>60.76 ± 12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>56.0</td>
<td>70.5</td>
<td>64.3</td>
<td>65.2</td>
<td>0.107</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>29.6 ± 5.3</td>
<td>27.8 ± 4.9</td>
<td>26.1 ± 4.9</td>
<td>27.9 ± 6.6</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt;25 kg/m² (%)</td>
<td>19.5</td>
<td>33.9</td>
<td>43.8</td>
<td>30.3</td>
<td>0.024</td>
</tr>
<tr>
<td>25 - 29.9 kg/m² (%)</td>
<td>41.5</td>
<td>34.7</td>
<td>39.6</td>
<td>39.5</td>
<td>0.024</td>
</tr>
<tr>
<td>≥30 kg/m² (%)</td>
<td>39.0</td>
<td>31.5</td>
<td>16.7</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>OVID-19 vaccine (%)</td>
<td>34.4</td>
<td>10.1</td>
<td>30.4</td>
<td>4.3</td>
<td>&lt;</td>
</tr>
<tr>
<td>Doses of vaccine (n)</td>
<td>1.6 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>1.7± 0.6</td>
<td>2.0 ± 0.0</td>
<td>0.228</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>45.6</td>
<td>44.1</td>
<td>50.0</td>
<td>53.2</td>
<td>0.592</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>23.2</td>
<td>35.4</td>
<td>26.0</td>
<td>41.6</td>
<td>0.026</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>0.0</td>
<td>4.8</td>
<td>8.0</td>
<td>9.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Days in Hospital (d)</td>
<td>7 (5-11)</td>
<td>9 (6-14)</td>
<td>13 (8-23)</td>
<td>15 (9-24)</td>
<td>&lt;</td>
</tr>
<tr>
<td>Mechanical Ventilation %</td>
<td>33.3</td>
<td>23.1</td>
<td>48.4</td>
<td>71.2</td>
<td>&lt;</td>
</tr>
<tr>
<td>Vasopressor use (%)</td>
<td>6.4</td>
<td>13.3</td>
<td>43.1</td>
<td>52.5</td>
<td>&lt;</td>
</tr>
<tr>
<td>Dimer (µg/mL)</td>
<td>0.30 (0.20-0.60)</td>
<td>0.51 (0.30-0.90)</td>
<td>0.66 (0.30-1.67)</td>
<td>0.95 (0.42-2.13)</td>
<td>&lt;</td>
</tr>
<tr>
<td>Blood Urea Nitrogen (mg/dL)</td>
<td>15.5 (12.0-21.1)</td>
<td>19.9 (14.9-33.1)</td>
<td>26.4 (20.5-46.8)</td>
<td>30.0 (18.9-56.5)</td>
<td>&lt;</td>
</tr>
<tr>
<td>Creat Dehydrogenase (IU/L)</td>
<td>319 (245-422)</td>
<td>352 (249-478)</td>
<td>370 (275-475)</td>
<td>412 (279-555)</td>
<td>0.012</td>
</tr>
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<tr>
<td>C-reactive protein (mg/dL)</td>
<td>14.6 (6.5-20.6)</td>
<td>15.1 (6.8-21.7)</td>
<td>15.8 (7.2-22.4)</td>
<td>17.8 (11.8-28.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>erritin (ng/mL)</td>
<td>472 (271-750)</td>
<td>533 (325-1105)</td>
<td>725 (243-1253)</td>
<td>802 (484-1342)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.6 ± 2.4</td>
<td>14.6 ± 2.9</td>
<td>13.2 ± 2.9</td>
<td>13.1±3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine at admission (mg/dL)</td>
<td>0.8 ± 0.3</td>
<td>1.4 ± 1.8</td>
<td>2.0 ± 3.2</td>
<td>2.7±4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Asal serum creatinine ng/dL</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 1.2</td>
<td>1.1 ± 1.4</td>
<td>1.1±1.5</td>
<td>0.445</td>
</tr>
<tr>
<td>Hydric balance &gt; 1000 cc (%)</td>
<td>66.4</td>
<td>46.8</td>
<td>58.9</td>
<td>70.7</td>
<td>&lt; 0.001</td>
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<tr>
<td>Hemodialysis (%)</td>
<td>0.0</td>
<td>2.6</td>
<td>7.0</td>
<td>31.0</td>
<td>&lt; 0.001</td>
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<tr>
<td>Peritoneal dialysis (%)</td>
<td>0.0</td>
<td>0.9</td>
<td>4.7</td>
<td>2.9</td>
<td>0.141</td>
</tr>
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Table 2. Cox proportional hazard model of Fluid Overload and the risk for 28-day mortality, development of Acute Kidney Injury (AKI) stage 3 and need for Renal Replacement Therapy.
<table>
<thead>
<tr>
<th>Model</th>
<th>28-day Mortality</th>
<th>AKI 3</th>
<th>Renal Replacement Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.098 (1.280-3.439)</td>
<td>0.003</td>
<td>1.886 (1.202-2.961)</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.358 (1.358-4.096)</td>
<td>0.002</td>
<td>2.043 (1.234-3.382)</td>
</tr>
<tr>
<td>Model 3</td>
<td>3.077 (1.670-5.669)</td>
<td>&lt;0.001</td>
<td>2.566 (1.499-4.393)</td>
</tr>
<tr>
<td>Model 4</td>
<td>3.014 (1.573-5.777)</td>
<td>&lt;0.001</td>
<td>3.159 (1.708-5.840)</td>
</tr>
</tbody>
</table>

Model 1 was adjusted by age, sex, and Body Mass Index; model 2 included model 1 plus type 2 diabetes, hypertension, chronic kidney disease, mechanical ventilation, vasopressor use; and model 3 included model 2 plus serum levels of D-dimer, lactic dehydrogenase, C-reactive protein, and ferritin.

**Figures**
Figure 1


Figure 2

Figure 3
Cumulative survival of 28-day mortality in hospitalized patients with Covid-19. Left panel included all 412 patients; Right panel only included the 287 patients who developed Acute Kidney Injury (AKI). A and B: Kaplan Meier plots for 28-day mortality according to Global Fluid Overload balances. C and D: Kaplan Meier plots for 28-day mortality according to categorical >1000 cc Global Fluid Overload.

Supplementary Files

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- GraphicalAbstract.jpeg