Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Biochemistry tests in hospitalized COVID-19 patients: Experience from a Canadian tertiary care centre

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) has variable clinical presentation, from asymptomatic to severe disease leading to death. Biochemical markers may help with management and prognostication of COVID-19 patients; however, their utility is still under investigation.

Methods: A retrospective study was conducted to evaluate alanine aminotransferase, C-reactive protein (CRP), ferritin, lactate, and high sensitivity troponin T (TnT) levels in 67 patients who were admitted to a Canadian tertiary care centre for management of COVID-19. Logistic, cause-specific Cox proportional-hazards, and accelerated failure time regression modelling were performed to assess the associations of initial analyte concentrations with in-hospital death and length of stay in hospital; joint modelling was performed to assess the associations of the concentrations over the course of the hospital stay with in-hospital death.

Results: Initial TnT and CRP concentrations were associated with length of stay in hospital. Eighteen patients died (27%), and the median initial TnT concentration was higher in patients who died (55 ng/L) than those who lived (16 ng/L; $P < 0.0001$). There were no survivors with an initial TnT concentration > 64 ng/L. While the initial TnT concentration was predictive of death, later measurements were not. Only CRP had prognostic value with both the initial and subsequent measurements: a 20% increase in the initial CRP concentration was associated with a 14% (95% confidence interval (CI): 1–29%) increase in the odds of death, and the hazard of death increased 14% (95% CI: 5–25%) for each 20% increase in the current CRP value. While the initial lactate concentration was not predictive of death, subsequent measurements were.

Conclusion: CRP, lactate and TnT were associated with poorer outcomes and appear to be useful biochemical markers for monitoring COVID-19 patients.

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by exposure to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is responsible for an ongoing pandemic that has thus far resulted in over one hundred fifty million cases and more than three million deaths worldwide [1]. While most cases present with mild symptoms or no symptoms at all, some of those affected develop serious, potentially fatal illness. The overall case fatality rate in Canada during the first wave of the pandemic was 1.6% [2], with older patients dying at higher rates than younger patients [3,4].

Many studies have demonstrated that COVID-19 affects not only the respiratory tract, but also other systems and organs, including the heart, liver, and gastrointestinal system, for example. Studies have demonstrated that several important hematological and biochemical markers are altered in patients with COVID-19 [5–7]. These biomarkers may be important for prognostication and management of patients, particularly those with co-morbidities and/or a severe course of the disease [8].

Patients presenting with severe COVID-19 (which may result in admission to the intensive care unit (ICU) and/or death) tend to have higher concentrations of pro-inflammatory cytokines (interleukins (IL): IL-2, IL-6, IL8, and IL-10) [9,10]; increased inflammatory markers (C-reactive protein (CRP), erythrocyte sedimentation rate, and ferritin) [11–13]; and other biochemical markers (alanine aminotransferase (ALT), bilirubin, high sensitivity cardiac troponin I (TnI) or T (TnT), creatinine, creatine kinase, lactate dehydrogenase, and urea), but lower

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albumin levels [5,6,14]; lower lymphocyte and platelet counts [15,16]; and increased D-dimer levels and prothrombin time [17,18]. Even though lactate, a marker of tissue perfusion perturbation, is frequently measured to assess septic patients [19], limited information exists on its utility in COVID-19 patients. The prognostic value of the aforementioned biochemical markers in COVID-19 patients is still under investigation and, to our knowledge, there are limited published data on utility of these biochemical markers in a Canadian population with COVID-19. In this study, we aimed to characterize the impact of factors, such as age and ICU admission, on outcome, as well as assess the potential prognostic role of ALT, CRP, ferritin, TnT, and lactate in patients hospitalized for COVID-19.

2. Methods

2.1. Patients

This retrospective study received ethics approval from the Lawson Health Research Institute and Western University Research Ethics Boards. Results of RT-PCR testing for SARS-CoV-2 virus infectivity from nasopharyngeal swabs were provided by the Microbiology Laboratory at London Health Sciences Centre (LHSC) between March 17, 2020 and June 30, 2020. From this list, patients who tested positive were identified, and chart reviews were performed to identify which of these patients were admitted to hospital at LHSC (Victoria Hospital or University Hospital, London, Ontario, Canada) for their SARS-CoV-2 infection. Three patients who were believed by the clinicians to have a SARS-CoV-2 infection based on clinical assessment but whose SARS-CoV-2 test results were 'inconclusive' (rather than positive or negative) were also included. In total there were 67 patients included in the study. There were 16 patients admitted to ICU, and all but two of these patients were admitted directly to ICU without being admitted to another ward first.

2.2. Laboratory testing and data collection

The ALT, CRP, and lactate testing were performed on Roche cobas c501 and c702 instruments. Ferritin and TnT testing were performed on Roche cobas e801 instruments. In addition to testing with the Roche assay, lactate was also measured as part of blood gas analysis on Instrumentation Laboratory GEM Premier 4000 analyzers either in the core laboratory or by point-of-care testing in the ICU. All lactate results from various instruments/locations were treated as equivalent and merged, as there were no known biases between them. For TnT, the 99th percentile of the upper reference limit (URL) from healthy individuals is 14 ng/L.

Data on the ALT, CRP, ferritin, TnT, and lactate test results for the study patients were obtained from the laboratory information system, Cerner Millennium. Only results for the hospital visits during which the patients were admitted were included, which included testing performed while patients were in the emergency department. Most patients (84%) had at least one of the tests of interest performed while they were in the emergency department. The initial ALT, CRP, ferritin, lactate, and TnT values for each patient during their hospital stay were determined from the collected data. Average concentrations for each of these analytes were also determined when the test was performed more than once on a patient within a calendar day. For four patients who had concentrations below the assay reportable limits for some of the analytes of interest, the analyte concentrations were changed to the corresponding limit value.

2.3. Statistical analysis

Descriptive statistics were computed to characterize the study population in terms of its distribution by age and sex of the patients and the initial concentrations of the analytes of interest. Mann-Whitney *U* tests were used to test for differences in the distributions of continuous variables between groups, such as the age of patients in ICU vs. not in ICU, the age of patients who died in hospital vs. survived, or analyte concentrations between patients who died in hospital vs. survived. Fisher's exact tests were used to test for differences in the distributions of binary variables between two groups, such as the proportions of patients in ICU or not in ICU who died in hospital. A receiver operator characteristic (ROC) curve was generated to depict the estimated 'sensitivity' and 'specificity' of the TnT test result (over a range of possible cutoff points applied to initial TnT concentration) vis-à-vis in-hospital death.

The relationship between the length of stay in hospital and the initial value of the tests of interest was estimated using an accelerated failure time model, in which in-hospital deaths were treated as competing events. A natural logarithm transformation was used for both the length of stay and the initial test values, and a Weibull distribution was assumed for the log-transform of the length of stay. Logistic regression analyses were performed for death as a binary outcome to test for its association with initial test values for the analytes of interest, with adjustment of age and sex. The odds ratios were estimated from the logistic regression models. To test the associations between the test values measured repeatedly over time (rather than just the initial analyte values) and in-hospital death, a joint model of longitudinal data of each test and the time to death in the presence of discharge as a competing event was employed [20]. In the joint model, the longitudinal measurements of each analyte were modelled by the mixed-effects model allowing the intercept and the slope for time variable to vary across patients, where natural-logarithm transforms of the test results were used as the dependent variable and the time represents the days since the initial test was performed. These models were fitted with adjustment for age and sex. Then, the in-hospital mortality was modelled by cause-specific Cox proportional-hazards regression with adjustment of age and sex and jointly with the analytes measured longitudinally to evaluate their effects with in-hospital death, where the baseline hazard function was approximated by B-splines. The association between the current value of the analyte and in-hospital mortality was estimated from the joint models.

All analyses were performed using the statistical software R (version 3.6.1) or GraphPad Prism 8, and $P < 0.05$ was considered statistically significant.

3. Results

Table 1 depicts the age and sex of the patients and the initial concentrations of the analytes of interest.

For the patients who were discharged alive, discharge occurred

Table 1
Descriptive statistics. Age, sex, and initial concentrations of the analytes of interest.

	All Patients (n = 67)	Reference Intervals Applicable to Study Patients
Age, Years (Median (IQR))	70 (26)	
Female (n (%))	30 (45%)	
Initial ALT Concentration (U/L) (Median (IQR))	30 (41)	Male: ≤41 Female: ≤33
Initial CRP Concentration (mg/L) (Median (IQR))	110.6 (144.1)	<5.0
Initial Ferritin Concentration (μg/L) (Median (IQR))	738 (1576)	Male: 20-<60 years: 30–400 ≥60 years: not available Female: 15-<19 years: 4–114 19-<60 years: 13–150 ≥60 years: not available
Initial TnT Concentration (ng/L) (Median (IQR))	18 (29)	≤14
Initial Lactate Concentration (mmol/L) (Median (IQR))	1.6 (0.9)	0.5–2.2

0–205 days after admission (there was one patient who was discharged on the same day admission occurred), with a median (interquartile range (IQR)) hospital stay of 11 (33) days. In the patients who died in hospital, death occurred 3–36 days after admission, with a median (IQR) period of 10 (15) days.

As shown in Table 2, patients admitted to ICU (median age, years (IQR): 58 (16)) were younger than patients who were not admitted to ICU (74 (29)) ($P = 0.02$). This is also represented in Fig. 1A. In addition, patients who died (median age, years (IQR): 74 (19)) were older than patients who were discharged (67 (24); $P = 0.03$). As shown in the cumulative incidence plot in Fig. 1B, patients under 60 years of age had a lower in-hospital mortality rate ($P = 0.02$) than patients aged 60 years or older.

Sixteen of 67 patients were admitted to ICU, resulting in an ICU admission rate of 24%. As shown in Table 2, 18 of 67 patients died in hospital, resulting in an in-hospital death rate of 27%. Of the 16 patients admitted to ICU, seven died, resulting in an in-ICU death rate of 44%, while in 51 patients not admitted to ICU, eleven died, resulting in a death rate of 22% ($P = 0.1$).

Not all patients had all the tests of interest performed during their stay in hospital. Sixty-four out of 67 patients had ALT tested (96%), 65 had CRP tested (97%), 56 had ferritin tested (84%), 60 had TnT tested (90%), and 64 had lactate tested (96%). In patients who had the analytes of interest tested, most (82% for ferritin, 92–98% for the rest) of the initial tests were performed within one day of admission.

Looking at the results of the analytes of interest, the initial ALT, CRP, ferritin, TnT, and lactate concentrations had regression coefficients in the accelerated failure models of –0.08, 0.33, 0.08, 0.62, and 0.22, respectively, ($P = 0.7$, 0.004, 0.6, 0.005, and 0.6, respectively) for their associations with the length of stay in hospital after adjustment for age and sex (Fig. 2). Specifically, for every 20% increase in the initial CRP value, the average length of stay increased 6% (95% confidence interval (CI): 2–11%; $P = 0.004$). For every 20% increase in the initial TnT value, the average length of stay increased 12% (95% CI: 3–21%, $P = 0.005$).

As shown in Fig. 3, the initial TnT concentrations were higher ($P < 0.0001$) in patients who died (median 55 ng/L) than those who were discharged (16 ng/L). Modelling death as a binary outcome against initial TnT values using logistic regression, after adjusting for age and sex, the estimated odds ratio was 1.37 (95% CI: 1.12–1.68; $P = 0.002$) for a 20% increase in the initial TnT concentration, indicating a 37% increase in the odds of in-hospital death. For a 20% increase in the initial CRP concentration, the estimated odds ratio was 1.14 (95% CI: 1.01–1.30; $P = 0.03$), indicating a 14% increase in the odds of death. The odds ratios for the associations of 20% increases in initial ALT, ferritin, and lactate concentrations with in-hospital death were 0.98 (95% CI: 0.86–1.12; $P = 0.7$), 1.05 (95% CI: 0.94–1.18; $P = 0.4$), and 1.17 (95% CI: 0.87–1.56$P = 0.3$), respectively.

The ROC curve analysis of initial TnT values had an area under the curve of 0.83 (95% CI: 0.72–0.95; $P = 0.0001$) and identified a cutoff of > 34 ng/L as the concentration with the highest Youden index (sum of sensitivity and specificity estimates − 1) for in-hospital death (Fig. 4). The sensitivity estimate at this cutoff was 67% (95% CI: 42–85%) and the specificity estimate was 84% (95% CI: 71–92%). A specificity estimate of 100% (95% CI: 92–100%) was achieved at an initial TnT cutoff of > 64 ng/L, which had a sensitivity estimate of 47% (95% CI: 25–70%). Thus, none of the patients who survived had an initial TnT concentration > 64 ng/L. In the 18 patients who died, TnT was not tested in three and the initial TnT concentration was > 64 ng/L in seven.

The longitudinal modelling of repeated measurements of the analytes demonstrated that ALT, CRP and ferritin values tended to decrease approximately 2%, 1% and 1%, respectively, for one-year increases in age, whereas TnT and lactate values increased 3% and 0.3%, respectively, for one-year increases in age ($P = 0.03$ for lactate and < 0.001 for the rest). It also showed that CRP, ferritin, and lactate values tended to decrease over time in patients during their stay in hospital (approximately 8%, 3% and 0.6% decreases per day, respectively; $P < 0.0001$ for all), whereas TnT values tended to increase 0.5% per day ($P = 0.03$). The median (IQR) number of tests performed in each patient was 2 (3) for ALT, 4 (7) for CRP, 2 (5) for ferritin, 4 (5) for TnT, and 3 (16) for lactate. When joint modelling of longitudinal measurements of the analytes and time to in-hospital death was performed, the associations between ALT, ferritin, and TnT concentrations over the course of the hospital stays with in-hospital death were not statistically significant: 1% decrease (95% CI: −17–19%; $P = 0.9$), 6% increase (95% CI: −7–20%; $P = 0.4$) and 2% increase (95% CI: −2–7%; $P = 0.3$), respectively, in the hazard of in-hospital death for each 20% increase in analyte concentration. CRP and lactate values were associated with the hazard of in-hospital death. A 20% increase in the current value of CRP was found to be associated with a 14% (95% CI: 5–25%; $P = 0.003$) increase in a patient's hazard of in-hospital death. A 20% increase in the current value of lactate was found to be associated with a 99% (95% CI: 17–241%; $P = 0.01$) increase in a patient's hazard of in-hospital death.

Table 2
Association of age with ICU admission or death, and association of ICU admission with death rate. Mann-Whitney *U* tests were performed to determine if older patients were more likely to be admitted to ICU or to die. A Fisher's exact test was performed to determine if the death rate was higher in patients admitted to ICU than in patients who were not in ICU.

	Not in ICU (n = 51)	In ICU (n = 16)	*P* Value	Discharged (n = 49)	Deceased (n = 18)	*P* Value
Age, Years (Median (IQR))	74 (29)	58 (16)	0.02*	67 (24)	74 (19)	0.03*
Death Rate, n (%)	11 (22%)	7 (44%)	0.1			

4. Discussion

Despite several reviews and *meta*-analyses evaluating the importance of biomarkers for the monitoring and prognostication of COVID-19 patients, the role of biochemical markers in this disease is still under investigation. To date there are also limited data on the commutability of results published from other countries to the Canadian patient population. Therefore, we performed a retrospective study to evaluate several key biochemical markers (ALT, CRP, ferritin, TnT, and lactate) in SARS-CoV-2 positive patients who were admitted at LHSC during the first wave of the pandemic (March 17, 2020 to June 30, 2020). Data on a total of 67 patients were evaluated. The rationale for biochemical testing includes monitoring disease course and recognizing patients who are likely to have poorer prognoses [8]. The International Federation of Clinical Chemistry and Laboratory Medicine, a global medical/scientific organization involved in standardizing practices in laboratory medicine, has recently published interim guidelines on biochemical/hematological testing of COVID-19 patients [8]. Of the dozen biochemical markers presented in the guideline, we selected ALT, CRP, ferritin, and TnT to evaluate, in order to assess the acute phase and inflammatory state of the patients, along with multiorgan involvement (e.g., liver and heart). There are limited data on lactate, a sepsis marker commonly used to assess tissue perfusion perturbation [19], in COVID-19 patients; thus, we assessed its utility also.

In terms of length of stay in hospital, we observed that increased initial TnT values were associated with longer time until discharge. The initial concentrations of TnT were also significantly associated with in-hospital death, whereby a 20% increase in the initial TnT concentration was associated with a 37% increase in the odds of in-hospital death. The initial TnT levels were significantly higher in patients who died than in those who were discharged, and none of the patients who survived had an initial TnT concentration > 64 ng/L. Interestingly, TnT concentrations over the course of the patients' stay in hospital did not show

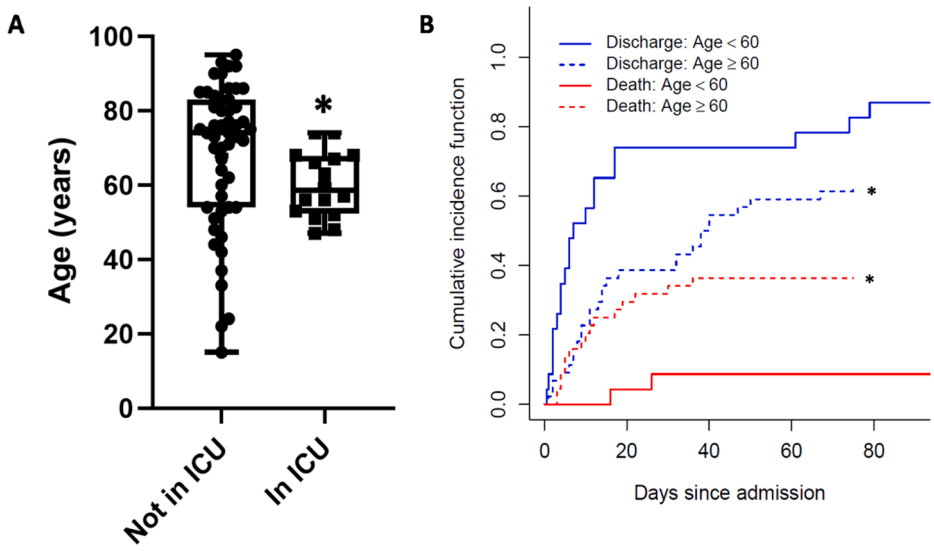

Fig. 1. Box and whisker plot comparing age distributions of patients who were not admitted to ICU and patients who were admitted to ICU (A). *, $P < 0.05$ according to Mann-Whitney *U* test. Cumulative incidence plot treating discharge and death as competing events (B). The impact of age < 60 years or ≥ 60 years on discharge or death was determined. *, $P < 0.05$.

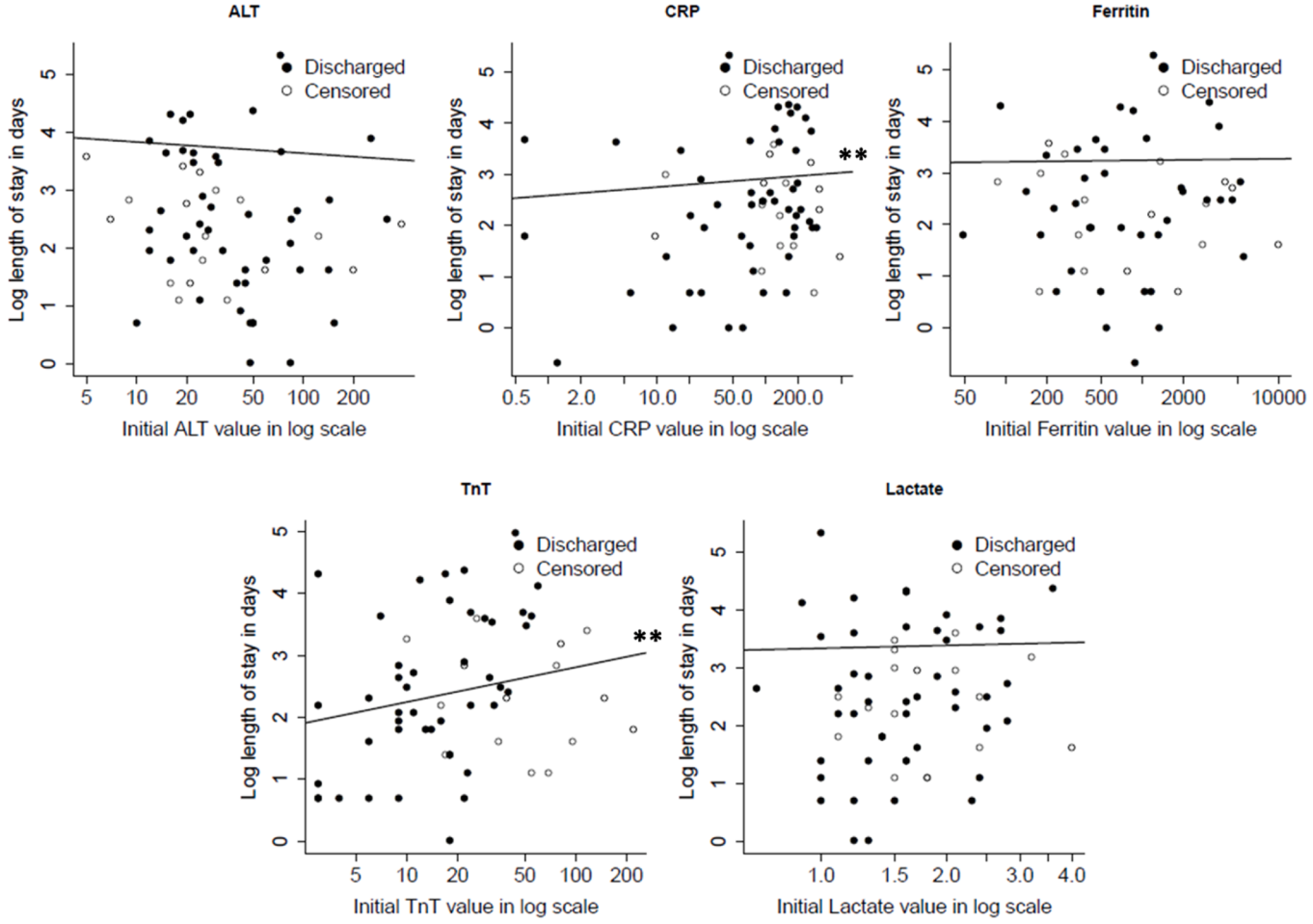

Fig. 2. Correlation of length of stay in hospital with the initial value of ALT, CRP, ferritin, TnT, or lactate. An accelerated failure time model was used to account for the length of stay being right censored due to death. A natural logarithm transformation was used for both the time and initial analyte variables and a Weibull distribution was assumed for the length of stay. **, $P < 0.01$ with adjustment for age and sex.

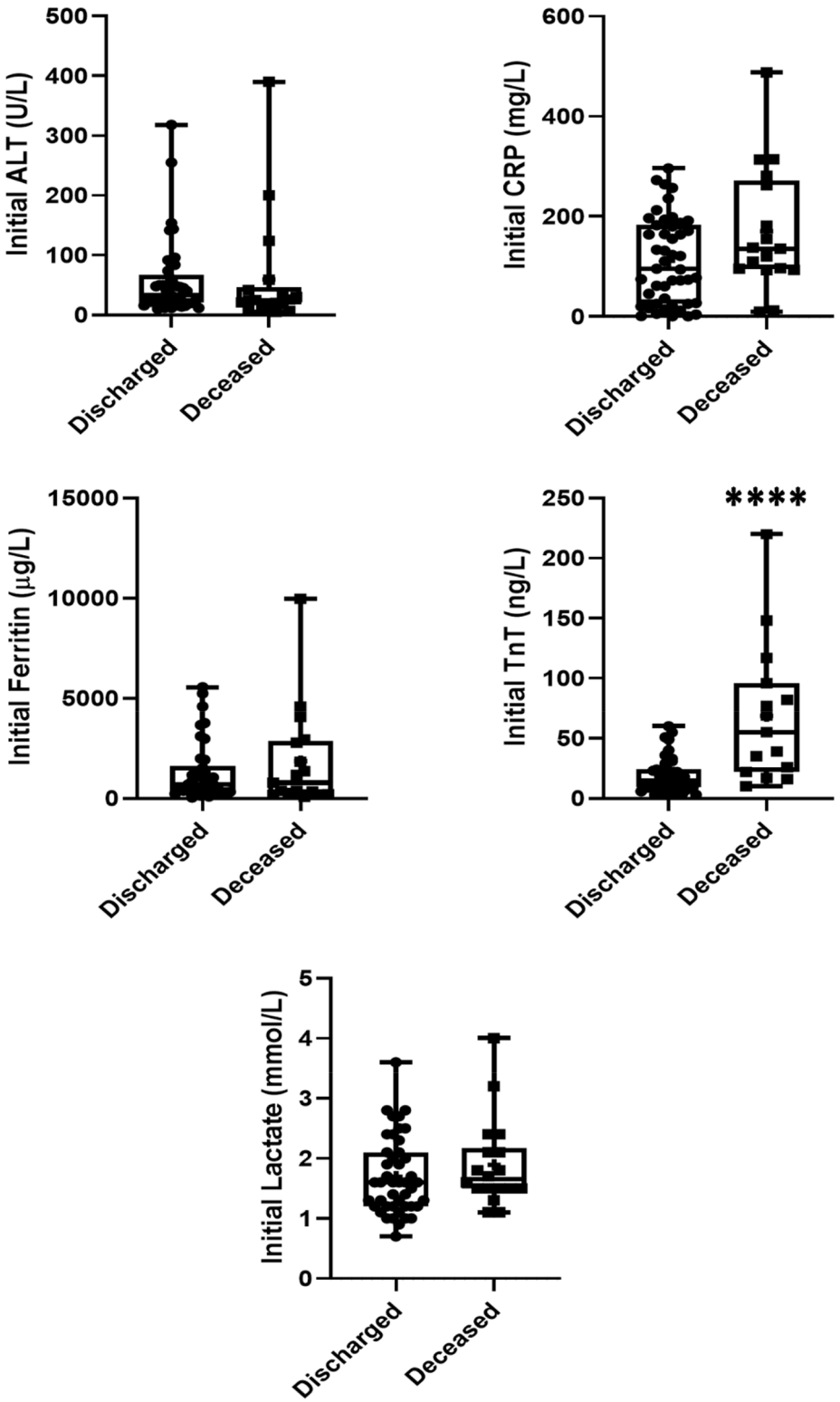

Fig. 3. Box and whisker plots comparing initial concentrations of ALT, CRP, ferritin, TnT, and lactate in patients who survived and were discharged to those in patients who died in hospital. ****, $P < 0.0001$ according to Mann-Whitney U test.

statistically significant associations with death, but rather it was the initial TnT that was most informative in terms of prognosis. Other studies have also found higher troponin values to be associated with poorer prognosis in COVID-19 patients [21–25]. Zhou *et al.* demonstrated that a cutoff of 28 ng/L for high sensitivity TnI was associated with significant in-hospital mortality with an odds ratio of 80 (95% CI: 10–620) [23]. In addition, De Michieli *et al.* demonstrated that a single overall cutoff of high sensitivity TnI of 26 ng/L was associated with death with an overall area under the curve of 0.811, and the authors also concluded that peak high sensitivity TnI concentration was not more informative than the initial value [26], similar to our observation. Interpretation of cardiac troponin levels in COVID-19 patients must be done with caution as some studies are based on TnT and others on TnI, some are based on high sensitivity assays while others are not, and some

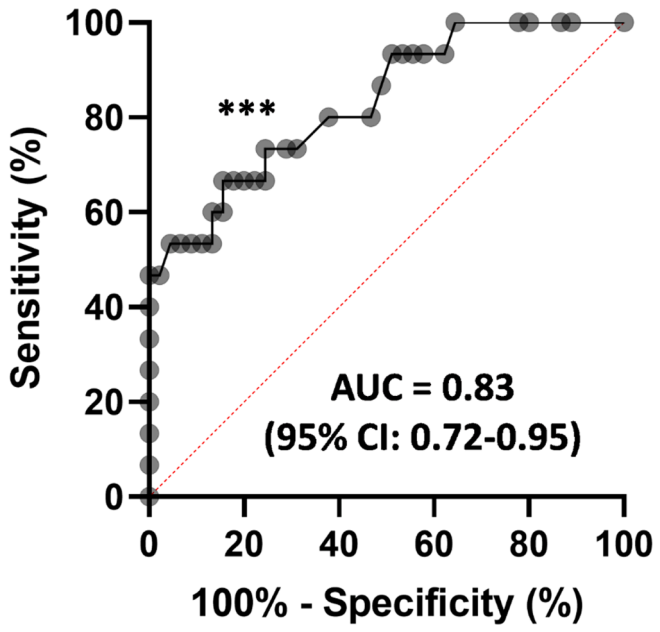

Fig. 4. ROC curve analysis of initial TnT concentration with regard to death. AUC, area under the curve; ***, $P < 0.001$.

of the available literature does not report the manufacturer of the assay or the 99th percentile of the URL, thus making extrapolation and interpretation of data difficult [25]. Nonetheless, overwhelming evidence exists to demonstrate that cardiac troponin appears to be elevated in patients with severe COVID-19, most likely resulting from myocardial dysfunction caused by the infection or by the host response [27–29]. Myocardial injury could also be caused by COVID-19-related type 1 or 2 myocardial infarcts, myocarditis, cardiomyopathy, microvascular dysfunction, arrhythmias, coagulopathies, or cytokine storm [25,30,31].

Similar to TnT, we observed that increased initial CRP values were significantly associated with longer time until discharge and in-hospital death. A 20% increase in the initial CRP concentration was associated with a 14% increase in the odds of death. Furthermore, CRP concentrations throughout the hospital stay continued to relate to the occurrence of death. As the current CRP concentration increased by 20%, the hazard for in-hospital death increased by 14%. Several other studies have also demonstrated that CRP was positively correlated with disease severity, morbidity, and mortality in COVID-19 patients [11,32–36], and that CRP was a good predictor of adverse outcome [36].

With regard to lactate, while the initial lactate concentrations were not associated with increased mortality, the lactate concentrations over the course of the hospital stay were associated with death. As the current lactate concentration increased by 20%, the hazard for in-hospital death increased by 99%. This suggests that the tissue perfusion perturbation was worsening as patients became more ill from the disease. This is not surprising as patients with acute respiratory distress syndrome and sepsis often encounter hyperlactatemia and tend to have poor prognosis [19,37]. Another study demonstrated that a delta arterial-central venous lactate (with higher lactate in the arterial sample than in the central venous sample) was higher in severely ill and mechanically ventilated COVID-19 patients and was associated with poorer prognosis [38].

We did not observe notable changes with respect to ALT or ferritin in our study, despite several studies indicating increased association of liver injury and acute phase response in COVID-19 patients [13,39]. We speculate that liver injury in COVID-19 patients may occur due to a number of mechanisms, such as direct hepatocellular injury from the SARS-CoV-2 virus, hepatocytotoxicity resulting from various medications used to manage the patient, the presence of a hyperinflammatory syndrome, acute respiratory distress syndrome-related hypoxic liver injury, or hemodynamic instability, which could add to the variability of data reported for liver injury in COVID-19 patients [40,41]. A recent review reported that out of 128 studies, only one case study showed severe liver failure to be associated with COVID-19, whereas the majority of the studies demonstrated mild to moderate liver injuries [42]. This same study also concluded that liver failure was exceedingly rare and that high (e.g., > 10x URL) aminotransferase levels were an uncommon phenomenon in COVID-19 patients [42]. Furthermore, many published studies evaluated aspartate aminotransferase (AST) as an assessment of liver injury [43]. Because AST is not liver-specific, elevated levels may reflect injury of other organs (e.g., heart, muscle, kidney, or brain), not just the liver. As for ferritin, being an acute phase reactant, we expected it to increase in concert with increased CRP levels; however, this was not the case in our study. Generally, ferritin levels have been observed to be mildly to moderately elevated in COVID-19 patients [44]. However, reports for this analyte appear to be variable also, as others have shown ferritin levels did not increase with the severity of COVID-19 infection [45].

Our analysis revealed that the patients who were admitted to the ICU were younger than the patients who were not admitted to ICU. In addition, patients aged < 60 years had a lower rate of in-hospital mortality compared to patients who were ≥ 60 years of age. We were surprised by these results and had expected older patients to be more likely to be admitted to ICU; however, our observations are consistent with a recent Canadian study by Papst *et al.* observing that ICU-related interventions and admissions were spread over a slightly younger age range, while hospitalizations were uniformly spread across a wide age range and mortality was skewed to the older population [3]. Another study observed older aged patients were more likely to be admitted to the ICU [46], while others observed no difference in the age of patients admitted to ICU [47,48]; thus, data on this aspect remain variable. There may be regional differences in the decisions about which patients to admit to ICU that could account for differences in observations between the studies. Others have also documented that older patients, particularly those ≥ 65 years of age, are more susceptible to morbidity and mortality from COVID-19 [4,49]; thus, our data are consistent with published literature in this regard. We calculated an ICU admission rate of 24% and an ICU mortality rate of 44%; the mortality rate in patients not admitted to the ICU was lower at 22%, resulting in an overall in-hospital mortality rate of 27%. The higher mortality rate in patients admitted to ICU was expected, as it is assumed that patients with more severe disease and requiring a higher level of management would be more likely to be admitted to ICU. Our results are similar to studies from China, Italy, and USA that reported a mortality rate ranging from 23% to 62% in critically ill COVID-19 patients [50–53]. Our data are also consistent with a recent *meta*-analysis that demonstrated an overall ICU admission rate of 32% and an overall ICU mortality rate of 39% [54]. The ICU mortality rate in our study was higher than previously reported by Mitra *et al.* in another Canadian institution; this study reported an ICU death rate of 15%, however data on overall in-hospital mortality were not available [55].

5. Limitations

There are several limitations to note in this study. First, the number of participants (n = 67) represents a small sample size. We were limited to the number of COVID-19 patients who presented to our health centre during the time of this study. Second, not all patients received testing on all analytes (96%, 97%, 84%, 90%, and 96% of patients had ALT, CRP, ferritin, TnT, and lactate tested, respectively), and the period between presentation at the hospital and initial testing of each of the analytes was variable for the patients who did have the tests performed, as was the time between symptom onset and initial testing. Third, the patients were from a single centre and may not represent the patient demographics or practices found across other institutions in Canada. Fourth, other than

age and sex, we did not control for patient anthropometrics, comorbidities, or demographics in our analyses on the associations between analyte levels and patient outcomes. Fifth, we did not include other important biochemical analytes, such as creatinine for assessment of acute kidney injury in COVID-19 patients. Due to lack of foresight on the authors' part, our ethics approval did not include creatinine on the list of approved biochemical markers to be examined in this retrospective study. Lastly, the patients included in this study were those that were affected by the first wave of the pandemic, which largely affected the most vulnerable and susceptible populations (e.g., elderly individuals in long-term care homes or front-line workers in close proximity to one another or to infected individuals without appropriate personal protective equipment) and there was not a clear understanding of the disease in question. It will be interesting to see how these data reflect what happens in future waves of the pandemic.

6. Conclusion

In summary, in this retrospective study of 67 hospitalized COVID-19 Canadian patients, we observed that CRP, TnT, and lactate concentrations were associated with in-hospital death and longer time to discharge from hospital in COVID-19 patients. For TnT, the first measurement from the admission had more prognostic value than subsequent measurements; for CRP both initial and subsequent measurements had prognostic value; and for lactate, the concentrations over the course of the patients' stay in hospital showed a stronger association with patient outcome than the initial values. Larger, prospective studies are required to further evaluate the importance of these biochemical markers (and others) in the Canadian population affected by COVID-19.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] T.J.H. University, John Hopkins University Corona Resource Center, (n.d.). https://coronavirus.jhu.edu/.
[2] E. Abdollahi, D. Champredon, J.M. Langley, A.P. Galvani, S.M. Moghadas, Temporal estimates of case-fatality rate for COVID-19 outbreaks in Canada and the United States, Cmaj. 192 (2020) E666–E670, https://doi.org/10.1503/cmaj.200711.
[3] I. Papst, M. Li, D. Champredon, B.M. Bolker, J. Dushoff, D.J.D. Earn, Age-dependence of healthcare interventions for SARS-CoV-2 infection in Ontario, Canada, MedRxiv. (2020), https://doi.org/10.1101/2020.09.01.20186395.
[4] R. Pastor-Barriuso, B. Pérez-Gómez, M.A. Hernán, M. Pérez-Olmeda, R. Yotti, J. Oteo-Iglesias, J.L. Sanmartín, I. León-Gómez, A. Fernández-García, P. Fernández-Navarro, I. Cruz, M. Martín, C. Delgado-Sanz, N. Fernández De Larrea, J. León Paniagua, J.F. Muñoz-Montalvo, F. Blanco, A. Larrauri, M. Pollán, Infection fatality risk for SARS-CoV-2 in community dwelling population of Spain: Nationwide seroepidemiological study, BMJ. 371 (2020) 1–19, https://doi.org/10.1136/bmj.m4509.
[5] X. Deng, B. Liu, J. Li, J. Zhang, Y. Zhao, K. Xu, Blood, biochemical, characteristics, of, patients, with, coronavirus, disease,, (COVID-19): A systemic review and meta-analysis, Clin. Chem. Lab. Med. 58 (2020) (2019) 1172–1181, https://doi.org/10.1515/cclm-2020-0338.
[6] G. Lippi, M. Plebani, Laboratory abnormalities in patients with COVID-2019 infection, Clin. Chem. Lab. Med. 58 (2020) 1131–1134, https://doi.org/10.1515/cclm-2020-0198.
[7] M.K. Bohn, G. Lippi, A. Horvath, S. Sethi, D. Koch, M. Ferrari, C. Bin Wang, N. Mancini, S. Steele, K. Adeli, Molecular, serological, and biochemical diagnosis and monitoring of COVID-19: IFCC taskforce evaluation of the latest evidence, Clin. Chem. Lab. Med. 58 (2020) 1037–1052, https://doi.org/10.1515/cclm-2020-0722.
[8] S. Thompson, M.K. Bohn, N. Mancini, T.P. Loh, C. Bin Wang, M. Grimmler, K.Y. Yuen, R. Mueller, D. Koch, S. Sethi, W.D. Rawlinson, M. Clementi, R. Erasmus, M. Leportier, G.C. Kwon, M.E. Menezes, M.M. Patru, M. Gramegna, K. Singh, O. Najjar, M. Ferrari, G. Lippi, K. Adeli, A.R. Horvath, IFCC Interim Guidelines on Biochemical/Hematological Monitoring of COVID-19 Patients, Clin. Chem. Lab. Med. 58 (2020) 2009–2016. https://doi.org/10.1515/cclm-2020-1414.
[9] Y. Tang, J. Liu, D. Zhang, Z. Xu, J. Ji, C. Wen, Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies, Front. Immunol. 11 (2020) 1–13, https://doi.org/10.3389/fimmu.2020.01708.
[10] D.M. Del Valle, S. Kim-Schulze, H.H. Huang, N.D. Beckmann, S. Nirenberg, B. Wang, Y. Lavin, T.H. Swartz, D. Madduri, A. Stock, T.U. Marron, H. Xie, M. Patel, K. Tuballes, O. Van Oekelen, A. Rahman, P. Kovatch, J.A. Aberg, E. Schadt, S. Jagannath, M. Mazumdar, A.W. Charney, A. Firpo-Betancourt, D. R. Mendu, J. Jhang, D. Reich, K. Sigel, C. Cordon-Cardo, M. Feldmann, S. Parekh, M. Merad, S. Gnjatic, An inflammatory cytokine signature predicts COVID-19 severity and survival, Nat. Med. 26 (2020) 1636–1643, https://doi.org/10.1038/s41591-020-1051-9.
[11] G. Wang, C. Wu, Q. Zhang, F. Wu, B. Yu, J. Lv, Y. Li, T. Li, S. Zhang, C. Wu, G. Wu, Y. Zhong, C-reactive protein level may predict the risk of COVID-19 aggravation, Open Forum Infect. Dis. 7 (2020) 1–5, https://doi.org/10.1093/ofid/ofaa153.
[12] I. Lapić, D. Rogić, M. Plebani, M. Plebani, Erythrocyte, sedimentation, rate, is, associated, with, severe, coronavirus, disease,, (COVID-19): A pooled analysis, Clin. Chem. Lab. Med. 58 (2020) (2019) 1146–1148, https://doi.org/10.1515/cclm-2020-0620.
[13] X.W. Jenifer Gómez-Pastoraa, Mitchell Weiganda, M.Y. James Kima, Jacob Strayera, Andre F. Palmera, J.J. Maciej, Zborowskib, Chalmersa, Hyperferritinemia in critically ill COVID-19 patients – Is ferritin the product of inflammation or a pathogenic mediator? Clin. Chim. Acta. 509 (2020) 249–251.
[14] P.A. Kavsak, P.A. Kavsak, K. De Wit, A. Worster, Clinical chemistry tests for patients with COVID-19-important caveats for interpretation, Clin. Chem. Lab. Med. 58 (2020) 1142–1143, https://doi.org/10.1515/cclm-2020-0436.
[15] Y. Liu, W. Sun, Y. Guo, L. Chen, L. Zhang, S. Zhao, D. Long, L. Yu, Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study, Platelets. 31 (2020) (2019) 490–496, https://doi.org/10.1080/09537104.2020.1754383.
[16] Y. Zhang, X. Zeng, Y. Jiao, Z. Li, Q. Liu, M. Yang, J. Ye, Mechanisms involved in the development of thrombocytopenia in patients with COVID-19, Thromb. Res. 193 (2020) 110–115, https://doi.org/10.1016/j.thromres.2020.06.008.
[17] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, C. Clark, T. Iba, ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemost. 18 (2020) 1023–1026, https://doi.org/10.1111/jth.14810.
[18] M. Hardy, J. Douxfils, J.M. Dogné, S. Lessire, B. Chatelain, S. Testa, I. Gouin-Thibault, Y. Gruel, T. Lecompte, F. Mullier, Management of the thrombotic risk associated with COVID-19: What is the role of the hemostasis laboratory? Ann. Biol. Clin. (Paris) 78 (2020) 471–481, https://doi.org/10.1684/ABC.2020.1581.
[19] M. Singer, C.S. Deutschman, C. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G.R. Bernard, J.D. Chiche, C.M. Coopersmith, R.S. Hotchkiss, M. M. Levy, J.C. Marshall, G.S. Martin, S.M. Opal, G.D. Rubenfeld, T. Der Poll, J. L. Vincent, D.C. Angus, The third international consensus definitions for sepsis and septic shock (sepsis-3), JAMA - J. Am. Med. Assoc. 315 (2016) 801–810, https://doi.org/10.1001/jama.2016.0287.
[20] R.M. Elashoff, G. Li, N. Li, A joint model for longitudinal measurements and survival data in the presence of multiple failure types, Biometrics. 64 (2008) 762–771, https://doi.org/10.1111/j.1541-0420.2007.00952.x.
[21] G. Lippi, C.J. Lavie, F. Sanchis-Gomar, Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis, Prog. Cardiovasc. Dis. 63 (2020) (2019) 390–391, https://doi.org/10.1016/j.pcad.2020.03.001.
[22] M. Salvatici, B. Barbieri, S.M.G. Cioffi, E. Morenghi, F.P. Leone, F. Maura, G. Moriello, M.T. Sandri, Association between cardiac troponin I and mortality in patients with COVID-19, Biomarkers. 25 (2020) 634–640, https://doi.org/10.1080/1354750X.2020.1831609.
[23] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet. 395 (2020) 1054–1062, https://doi.org/10.1016/S0140-6736(20)30566-3.
[24] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19), JAMA Cardiol. 5 (2020) (2019) 811–818, https://doi.org/10.1001/jamacardio.2020.1017.
[25] P.A. Kavsak, O. Hammarsten, A. Worster, S.W. Smith, F.S. Apple, Cardiac Troponin Testing in Patients with COVID-19: A Strategy for Testing and Reporting Results Peter A Kavsak, Clin. Chem. 67 (2021) 107–113.
[26] L. De Michieli, L. Babuin, S. Vigolo, G. Berti De Marinis, A. Lunardon, F. Favretto, R. Lobo, Y. Sandoval, S.C. Bryant, D. Donato, M. Plebani, R. Vettor, S. Iliceto, V. Cianci, A.S. Jaffe, Using high sensitivity cardiac troponin values in patients with SARS-CoV-2 infection (COVID-19): The Padova experience, Clin. Biochem. 90 (2021) 8–14, https://doi.org/10.1016/j.clinbiochem.2021.01.006.
[27] B. Siripanthong, S. Nazarian, D. Muser, R. Deo, P. Santangeli, M.Y. Khanji, L. T. Cooper, C.A.A. Chahal, Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management, Hear. Rhythm. 17 (2020) 1463–1471, https://doi.org/10.1016/j.hrthm.2020.05.001.
[28] A. Akhmerov, E. Marbán, COVID-19 and the Heart, Circ. Res. (2020) 1443–1455, https://doi.org/10.1161/CIRCRESAHA.120.317055.
[29] J.J. Manson, C. Crooks, M. Naja, A. Ledlie, B. Goulden, T. Liddle, E. Khan, P. Mehta, L. Martin-Gutierrez, K.E. Waddington, G.A. Robinson, L. Ribeiro Santos,

E. McLoughlin, A. Snell, C. Adeney, I. Schim van der Loeff, K.F. Baker, C.J. A. Duncan, A.T. Hanrath, B.C. Lendrem, A. De Soyza, J. Peng, H. J'Bari, M. Greenwood, E. Hawkins, H. Peckham, M. Marks, T. Rampling, A. Luintel, B. Williams, M. Brown, M. Singer, J. West, E.C. Jury, M. Collin, R.S. Tattersall, COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study, Lancet, Rheumatol. 2 (2020) e594–e602, https://doi.org/10.1016/S2665-9913(20)30275-7.

[30] J.P. Lang, X. Wang, F.A. Moura, H.K. Siddiqi, D.A. Morrow, E.A. Bohula, A current review of COVID-19 for the cardiovascular specialist, Am. Heart J. 226 (2020) 29–44, https://doi.org/10.1016/j.ahj.2020.04.025.

[31] A.R. Chapman, A. Bularga, N.L. Mills, High-Sensitivity Cardiac Troponin Can Be an Ally in the Fight against COVID-19, Circulation. 141 (2020) 1733–1735, https://doi.org/10.1161/CIRCULATIONAHA.120.047008.

[32] M.S. Asghar, S.J. Haider Kazmi, N. Ahmed Khan, M. Akram, M. Hassan, U. Rasheed, S. Ahmed Khan, Poor Prognostic Biochemical Markers Predicting Fatalities Caused by COVID-19: A Retrospective Observational Study From a Developing Country, Cureus. 12 (2020) 1–17, https://doi.org/10.7759/cureus.9575.

[33] B.R. Sahu, R. Kishor, A. Padhi, A.K. Panda, C-reactive protein: A promising biomarker for poor prognosis in COVID-19 infection, Clin. Chim. Acta. 509 (2020) 91–94.

[34] C. Tan, Y. Huang, F. Shi, K. Tan, Q. Ma, Y. Chen, X. Jiang, X. Li, C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early, J. Med. Virol. 92 (2020) 856–862, https://doi.org/10.1002/jmv.25871.

[35] Q. Li, X. Ding, G. Xia, H.G. Chen, F. Chen, Z. Geng, L. Xu, S. Lei, A. Pan, L. Wang, Z. Wang, Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: A retrospective case-control study, EClinicalMedicine. 23 (2020), 100375, https://doi.org/10.1016/j.eclinm.2020.100375.

[36] X. Luo, W. Zhou, X. Yan, T. Guo, B. Wang, H. Xia, L. Ye, J. Xiong, Z. Jiang, Y. Liu, B. Zhang, W. Yang, Prognostic Value of C-Reactive Protein in Patients with Coronavirus 2019, Clin. Infect. Dis. 71 (2020) (2019) 2174–2179, https://doi.org/10.1093/cid/ciaa641.

[37] Q. Dai, S. Wang, R. Liu, H. Wang, J. Zheng, K. Yu, Risk factors for outcomes of acute respiratory distress syndrome patients: A retrospective study, J. Thorac. Dis. 11 (2019) 673–685, https://doi.org/10.21037/jtd.2019.02.84.

[38] G. Nardi, G. Sanson, L. Tassinari, G. Guiotto, A. Potalivo, J. Montomoli, F. Schiraldi, Lactate Arterial-Central Venous Gradient among COVID-19 Patients in ICU: A Potential Tool in the Clinical Practice, Crit. Care Res. Pract. 2020 (2020), https://doi.org/10.1155/2020/4743904.

[39] F. Lei, Y.M. Liu, F. Zhou, J.J. Qin, P. Zhang, L. Zhu, X.J. Zhang, J. Cai, L. Lin, S. Ouyang, X. Wang, C. Yang, X. Cheng, W. Liu, H. Li, J. Xie, B. Wu, H. Luo, F. Xiao, J. Chen, L. Tao, G. Cheng, Z.G. She, J. Zhou, H. Wang, J. Lin, P. Luo, S. Fu, J. Zhou, P. Ye, B. Xiao, W. Mao, L. Liu, Y. Yan, L. Liu, G. Chen, H. Li, X. Huang, B.H. Zhang, Y. Yuan, Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China, Hepatology. 72 (2020) 389–398, https://doi.org/10.1002/hep.31301.

[40] D. Jothimani, R. Venugopal, M.F. Abedin, I. Kaliamoorthy, M. Rela, COVID-19 and the liver, J. Hepatol. 73 (2020) 1231–1240, https://doi.org/10.1016/j.jhep.2020.06.006.

[41] A. Saviano, F. Wrensch, M.G. Ghany, T.F. Baumert, Liver disease and COVID-19: from Pathogenesis to Clinical Care, Hepatology. (2020), https://doi.org/10.1002/hep.31684.

[42] P. Kumar-M, S. Mishra, D.K. Jha, J. Shukla, A. Choudhury, R. Mohindra, H. S. Mandavdhare, U. Dutta, V. Sharma, Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis, Hepatol. Int. 14 (2020) 711–722, https://doi.org/10.1007/s12072-020-10071-9.

[43] C. Zhang, L. Shi, F.S. Wang, Liver injury in COVID-19: management and challenges, Lancet Gastroenterol. Hepatol. 5 (2020) 428–430, https://doi.org/10.1016/S2468-1253(20)30057-1.

[44] P.E. Taneri, S.A. Gómez-Ochoa, E. Llanaj, P.F. Raguindin, L.Z. Rojas, Z.M. Roa-Díaz, D. Salvador, D. Groothof, B. Minder, D. Kopp-Heim, W.E. Hautz, M. F. Eisenga, O.H. Franco, M. Glisic, T. Muka, Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis, Eur. J. Epidemiol. 35 (2020) 763–773, https://doi.org/10.1007/s10654-020-00678-5.

[45] A. Shah, J.N. Frost, L. Aaron, K. Donovan, H. Drakesmith, S.R. McKechnie, S. J. Stanworth, Systemic hypoferremia and severity of hypoxemic respiratory failure in COVID-19, Crit. Care. 24 (2020) 4–7, https://doi.org/10.1186/s13054-020-03051-w.

[46] L. Kim, S. Garg, A. O'Halloran, M. Whitaker, H. Pham, E.J. Anderson, I. Armistead, N.M. Bennett, L. Billing, K. Como-Sabetti, M. Hill, S. Kim, M.L. Monroe, A. Muse, A. L. Reingold, W. Schaffner, M. Sutton, H.K. Talbot, S.M. Torres, K. Yousey-Hindes, R. Holstein, C. Cummings, L. Brammer, A.J. Hall, A.M. Fry, G.E. Langley, Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET), Clin. Infect. Dis. 30329 (2020) (2019) 1–9, https://doi.org/10.1093/cid/ciaa1012.

[47] M. Nakeshbandi, R. Maini, P. Daniel, S. Rosengarten, P. Parmar, C. Wilson, J. M. Kim, A. Oommen, M. Mecklenburg, J. Salvani, M.A. Joseph, I. Breitman, The impact of obesity on COVID-19 complications: a retrospective cohort study, Int. J. Obes. 44 (2020) 1832–1837, https://doi.org/10.1038/s41366-020-0648-x.

[48] G. Suleyman, R.A. Fadel, K.M. Malette, C. Hammond, H. Abdulla, A. Entz, Z. Demertzis, Z. Hanna, A. Failla, C. Dagher, Z. Chaudhry, A. Vahia, O. Abreu Lanfranco, M. Ramesh, M.J. Zervos, G. Alangaden, J. Miller, I. Brar, Clinical Characteristics, Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit, JAMA Netw. Open. 3 (2020) (2019), e2012270, https://doi.org/10.1001/jamanetworkopen.2020.12270.

[49] M. O'Driscoll, G.R. Dos Santos, L. Wang, D.A.T. Cummings, A.S. Azman, J. Paireau, A. Fontanet, S. Cauchemez, H. Salje, Age-specific mortality and immunity patterns of SARS-CoV-2, Nature. (2020), https://doi.org/10.1038/s41586-020-2918-0.

[50] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan, Y. Shang, 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. 8 (2020) 475–481, https://doi.org/10.1016/S2213-2600(20)30079-5.

[51] G. Grasselli, A. Zangrillo, A. Zanella, M. Antonelli, L. Cabrini, A. Castelli, D. Cereda, A. Coluccello, G. Foti, R. Fumagalli, G. Iotti, N. Latronico, L. Lorini, S. Merler, G. Natalini, A. Piatti, M.V. Ranieri, A.M. Scandroglio, E. Storti, M. Cecconi, A. Pesenti, Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy, JAMA - J. Am. Med. Assoc. 323 (2020) 1574–1581, https://doi.org/10.1001/jama.2020.5394.

[52] P.K. Bhatraju, B.J. Ghassemieh, M. Nichols, R. Kim, K.R. Jerome, A.K. Nalla, A. L. Greninger, S. Pipavath, M.M. Wurfel, L. Evans, P.A. Kritek, T.E. West, A. Luks, A. Gerbino, C.R. Dale, J.D. Goldman, S. O'Mahony, C. Mikacenic, Covid-19 in Critically Ill Patients in the Seattle Region — Case Series, N. Engl. J. Med. 382 (2020) 2012–2022, https://doi.org/10.1056/nejmoa2004500.

[53] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, D.P. Barnaby, L.B. Becker, J.D. Chelico, S.L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z.M. Kozel, L.M. Marrast, J. N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area, JAMA - J. Am. Med. Assoc. 323 (2020) 2052–2059, https://doi.org/10.1001/jama.2020.6775.

[54] S.M. Abate, S.A. Ali, B. Mantfardo, B. Basu, Rate of intensive care unit admission and outcomes among patients with coronavirus: A systematic review and Meta-analysis, PLoS One. 15 (2020) 1–19, https://doi.org/10.1371/journal.pone.0235653.

[55] A.R. Mitra, N.A. Fergusson, E. Lloyd-Smith, A. Wormsbecker, D. Foster, A. Karpov, S. Crowe, G. Haljan, D.R. Chittock, H.D. Kanji, M.S. Sekhon, D.E.G. Griesdale, Baseline characteristics and outcomes of patients with COVID-19 admitted to intensive care units in Vancouver, Canada: a case series, Cmaj. 192 (2020) E694–E701, https://doi.org/10.1503/cmaj.200794.