Mini Review

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Blood lactate concentration in COVID-19: a systematic literature review

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Abstract: Coronavirus disease 2019 (COVID-19) is an infectious respiratory condition sustained by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which manifests prevalently as mild to moderate respiratory tract infection. Nevertheless, in a number of cases the clinical course may deteriorate, with onset of end organ injury, systemic dysfunction, thrombosis and ischemia. Given the clinical picture, baseline assessment and serial monitoring of blood lactate concentration may be conceivably useful in COVID-19. We hence performed a systematic literature review to explore the possible association between increased blood lactate levels, disease severity and mortality in COVID-19 patients, including comparison of lactate values between COVID-19 and non-COVID-19 patients. We carried out an electronic search in Medline and Scopus, using the keywords “COVID-19” OR “SARS-CoV-2” AND “lactate” OR “lactic acid” OR “hyperlactatemia”, between 2019 and present time (i.e. October 10, 2021), which allowed to identify 19 studies, totalling 6,459 patients. Overall, we found that COVID-19 patients with worse outcome tend to display higher lactate values than those with better outcome, although most COVID-19 patients in the studies included in our analysis did not have sustained baseline hyperlactatemia. Substantially elevated lactate values were neither consistently present in all COVID-19 patients who developed unfavourable clinical outcomes. These findings suggest that blood lactate monitoring upon admission and throughout hospitalization may be useful for early identification of higher risk of unfavourable COVID-19 illness progression, though therapeutic decisions based on using conventional hyperlactatemia cut-off values (i.e., 2.0 mmol/L) upon first evaluation may be inappropriate in patients with SARS-CoV-2 infection.

Keywords: COVID-19; lactate; lactic acid; SARS-CoV-2; systematic literature review.

Introduction

Coronavirus disease 2019 (COVID-19), a new life-threatening infectious pathology caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is generating dramatic clinical impacts worldwide, with substantial derangements in the organization of healthcare, society and economy. From a clinical perspective, COVID-19 is mainly characterized by lower respiratory tract infection, which, in some patients, may evolve into acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death [1].

Hyperlactatemia is traditionally associated with poor outcomes in critically ill patients [2], and lactate value is regarded as one of the most important biomarkers of illness severity in patients with sepsis [3]. Although COVID-19 is a predominantly pulmonary disorder, it is also associated with end organ injury, systemic dysfunction, thrombosis, and ischemia [4], so that baseline assessment and serial monitoring of blood lactate concentration may be at least theoretically useful in this clinical setting. Nonetheless, the association between blood lactate values and clinical outcome remains unclear in patients with SARS-CoV-2 infection. Here we report the results of a systematic review.
aimed at exploring the possible association between increased blood lactate levels, disease severity and mortality in COVID-19 patients, including a comparison of lactate values between COVID-19 and non-COVID-19 patients.

**Methods**

We carried out an electronic search in Medline (PubMed interface) and Scopus, using the keywords “COVID-19” OR “SARS-CoV-2” AND “lactate” OR “lactic acid” OR “hyperlactatemia”, between 2019 and present time (i.e. October 10, 2021), restricted to articles published in English. The reference list of all documents was also reviewed for identifying other potentially eligible documents. All resulting items were screened (title, abstract and full text, when available or necessary) by two of the authors (GC and GL), in order to capture observational, cross-sectional or prospective studies reporting data on lactate values at admission (or at the earliest time point during hospitalization) in COVID-19 patients with or without severe disease, as well as in non-survivors vs. survivors. Severe disease was clinically defined as patients needing intensive care unit (ICU) admission, mechanical ventilation, hospitalization, pneumonia or onset of critical symptoms (ARDS) and/or shock and/or presence of organ failure. All studies fulfilling this criteria were then included in a systematic literature review. Disagreements between authors with respect to study eligibility were resolved by discussion and consensus. Results of the review were organized into summary of findings tables.

**Results**

**Studies identification and characteristics**

A total number of 2,659 studies were initially identified by our search criteria, 1,112 of which were excluded for duplication among the two databases, whilst 1,528 were also excluded because they failed to report lactate values. Nineteen studies, totalling 6,459 patients, were finally included in our systematic review [5–23]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is shown in Figure 1, whilst the PRISMA checklist is available as Supplementary File 1. The characteristics of the included studies are reported in Tables 1–4. All reported blood lactate values were measured upon hospital admission or at the earliest time point immediately after hospitalization (i.e., within 24 h). Velavan et al. [10] measured blood lactate concentrations not only in hospitalized patients but also in COVID-19 outpatients in home quarantine. Two studies by Hokenek et al. [6] and Kalabin et al. [16] reported both severity and mortality as clinical endpoints in their cohorts.

**Evidence on COVID-19 disease severity**

In the study of Hokenek et al. [6], patients were classified according to their lactate concentration. The cut-off value was set at blood lactate concentration >2 mmol/L, and patients with elevated levels were found to have a higher rate of ICU admission (Table 1). Four additional studies (totalling 436 patients, 114 of whom (26.1%) with severe disease) compared blood lactate values in severe vs. non-severe cases [10, 16, 18, 19]. Velavan et al. [10], Kalabin et al. [16], and Chen et al. [18] found that patients with severe disease had higher blood lactate values compared to non-severe patients. Unlike these findings, Yang et al. [19] reported that patients with severe disease did not display higher blood lactate values compared to those with non-severe illness (Table 2).

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**Figure 1:** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram.
Evidence on COVID-19 mortality

In two of the studies which described the risk of death in patients with blood hyperlactatemia (cut-off value set at blood lactate concentration >2 mmol/L) [5, 6], the risk of death was found to be higher in COVID-19 patients with elevated blood lactate values (Table 1). Eleven additional studies compared blood lactate values in COVID-19 survivors vs. non-survivors (2,744 total patients, 671 (24.5%) died) [7–11, 13–17, 20]. In all such studies, non-survivors displayed higher levels of blood lactate compared with survivors (Table 3).

Blood lactate in COVID-19 and non-COVID-19 patients with pneumonia or ARDS

A total number of three studies (150 patients) measured blood lactate levels in COVID-19 pneumonia or ARDS, which were then compared with those measured in non-COVID-19 pneumonia or ARDS of different aetiologies [21–23]. Notably, blood lactate values were consistently found to be lower in patients with COVID-19 than in those without (Table 4).

Discussion

Lactate is the most important end product of anaerobic metabolism. Oxygen deprivation of tissue typically leads to lactate hyper-production, as pyruvate can no longer be oxidized in the Krebs cycle due to oxygen deficiency, and is thus converted to lactate [25]. Hyperlactatemia can emerge from several different causes, including tissue hypoxia in sepsis. However, it is important to note that the concentration of this biomarker should not be considered a direct measure of tissue perfusion [25]. Additionally, hyperlactatemia can be induced by medications such as metformin, propofol, and acetaminophen [26–28]. Predisposing factors to lactic acidosis with metformin are conditions that can be very commonly seen among hospitalized patients with COVID-19 (e.g. hypoperfusion or hypoxemia, such as acute or renal impairment, acute heart failure, acute pulmonary decompensation, and sepsis).

The Surviving Sepsis Campaign guidelines recommend monitoring blood lactate in patients with sepsis or septic shock, guiding resuscitation to decrease serum lactate in patients with elevated lactate level [29]. Accordingly, early lactate clearance-directed therapy is associated with lower mortality [30], thus providing some insights on...
whether blood lactate monitoring may be helpful in patients with COVID-19.

Patients with severe COVID-19 illness frequently develop interstitial (often bilateral) pneumonia, which may then progress into ARDS or, even worse, with development of a systemic disease, target organ injury, MOF and death in the most severe cases [31]. Currently, COVID-19 treatment guidelines suggest that patients with COVID-19 who require fluid resuscitation should be treated identical to those with septic shock [32], though such indication has not been directly related to blood lactate values.

The results of our systematic literature review unsurprisingly demonstrate that COVID-19 patients with worse outcomes often have higher blood lactate values than those with better outcomes early in disease course (Tables 1–3). However, careful analysis of the included
studies reveals a more complex and variable biochemical picture. Interestingly, in the study by Velavan et al. [10], who measured blood lactate concentration in COVID-19 hospitalized patients and in outpatients in home quarantine after receiving a diagnosis of SARS-CoV-2 infection, reported that blood levels were significantly lower in ambulatory than in hospitalized patients (Table 2). It is important to underpin that most COVID-19 patients in the studies included in our analysis did not have baseline hyperlactatemia and that substantially elevated blood lactate values were often absent in many COVID-19 patients who developed unfavourable clinical outcomes (Tables 1–3). This suggests that the pathogenesis of severe COVID-19 illness is multifactorial and in part independent from severe ischemia and hyperlactatemia. This hypothesis is confirmed by evidence that patients with COVID-19 pneumonia or ARDS present with lower blood lactate values compared to those with non-COVID-19 pneumonia or ARDS of different aetiologies (Table 4). It could hence be concluded that although an increased blood lactate value may be frequent in COVID-19 patients with unfavourable clinical progression, we should not expect to find the same values that are typically observed in severe pneumonia and/or sepsis (i.e., constantly >2–3 mmol/L). In keeping with this conclusion, Vassiliou et al. [9] measured blood lactate at ICU admission and then every day until day 14. Although these authors found that the time course of blood lactate values mirrored organ dysfunction, frank hyperlactatemia (i.e., >2 mmol/L) was prevalently found only before death, but still only present in less than half (i.e., 45%) of all patients who died with SARS-CoV-2 infection. Further important evidence comes from the study of Lardaro et al. [33], who retrospectively evaluated 542 COVID-19 patients with bacterial co-infection. In these patients, despite the fact that bacteremia was significantly associated with elevated blood lactate values, the clinical outcomes did not significantly differ between patients with and without bacteremia.

In conclusion, the results of our systematic literature review suggest that monitoring blood lactate in patients with SARS-CoV-2 infection upon admission and throughout hospitalization (especially in critical patients and/or those needing mechanical ventilation or intensive care) may be a useful tool for early prediction of higher risk of unfavourable disease progression. Nonetheless, therapeutic decisions based on using a conventional hyperlactatemia cut-off value (i.e., 2.0 or even 3.0 mmol/L) upon first evaluation may be inappropriate in patients with SARS-CoV-2 infection.

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References


Table 4: Lactate levels in patients with pneumonia and/or acute respiratory distress syndrome (ARDS), with or without coronavirus disease 2019 (COVID-19).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Type of study</th>
<th>COVID-19 patients with pneumonia or ARDS</th>
<th>Non-COVID-19 patients with pneumonia or ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoechter et al. [21]</td>
<td>Germany</td>
<td>Retrospective</td>
<td>Sample size 22, Age, mean: 64 (52–70), Sex: 19/3 (M/F), Lactate value: 1.1 (1.0–1.4)</td>
<td>Sample size 14, Age, mean: 49 (36–57), Sex: 9/5 (M/F), Lactate value: 2.1 (1.1–7.1)</td>
</tr>
<tr>
<td>Shi et al. [22]</td>
<td>France, Italy</td>
<td>Observational</td>
<td>Sample size 60, Age, mean: 64 (54–72), Lactate value: 1.6 (1.3–2.1)</td>
<td>Sample size 60, Age, mean: 62 (55–73), Lactate value: 2.2 (1.2–3.5)</td>
</tr>
<tr>
<td>Arina et al. [23]</td>
<td>London</td>
<td>Retrospective</td>
<td>Sample size 68, Age, mean: 62 (53–69), Lactate value: 5 (7%) patients had lactate &gt;2 mmol/L and concurrent vasopressor use</td>
<td>Sample size 87, Age, mean: 64 (52–75), Lactate value: 42 (48%) patients had lactate &gt;2 mmol/L and concurrent vasopressor use</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome.


Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2021-1115).