Mini Review

Giovanni Carpenè*, Davide Negrini, Brandon M. Henry, Martina Montagnana and Giuseppe Lippi

Homocysteine in coronavirus disease (COVID-19): a systematic literature review

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) is a life-threatening infectious disorder characterized by a sustained prothrombotic state. Since homocysteine is a potential biomarker of thrombotic diseases, the aim of this article is to provide an updated overview on the possible role played by hyperhomocysteinemia in influencing an unfavorable COVID-19 progression.

Methods: We carried out an electronic search in Medline (PubMed interface) using the keywords (“COVID-19” OR “SARS-CoV-2”) AND “homocysteine”, between 2019 and the present time, with no language restrictions, to identify all articles which explored the concentration of homocysteine in COVID-19 patients with or without unfavorable disease progression.

Results: Three studies, totaling 694 hospitalized COVID-19 patients, were included in our systematic review. Overall, the differences between the mean homocysteine values in non-severe vs. severe COVID-19 patients were always positive (i.e., 15.1%, 24.1% and 22.8%, generating a positive weight mean difference of 1.75 μmol/L (95%CI, 1.26–2.25 μmol/L; p=0.011), which translates into a cumulative difference of approximately ~1.2 μmol/L.

Conclusions: Despite the limited evidence that has been garnered so far, increased homocysteine levels may be a potentially useful marker for predicting the risk of unfavorable progression in patients with COVID-19.

Keywords: COVID-19; homocysteine; SARS-CoV-2; systematic literature review.

Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was been identified as the responsible pathogen for a new pneumonia-like illness, that has since been called coronavirus disease 2019 (COVID-19). This novel coronavirus appears to have emerged from the Chinese town of Wuhan, and has since spread all around the world to cause the worst pandemic outbreak of the last 100 years [1]. SARS-CoV-2 is responsible of severe illness characterized by a heterogeneous spectrum of clinical manifestations, from asymptomatic disease to severe pulmonary involvement (with pneumonia and/or acute respiratory distress syndrome; ARDS), up to systemic dissemination, leading in a certain number of subjects (i.e., around 2–5%) to multiple organ failure and death [2]. One aspect that is now clearly acknowledged is that COVID-19 is associated with inflammation and thrombosis [3], acting in synergy to trigger the so-called phenomenon of thromboinflammation [4]. Not surprisingly, many studies have such reported remarkably high rates of venous thromboembolism in patients with severe COVID-19 [5] despite the use of thromboprophylaxis [6]. Moreover, patients with severe forms of COVID-19 may also develop acute myocardial ischemia (infarction), cerebrovascular events, arterial thrombosis [7] or microthrombosis in multiple organs including the lungs [8].
activation (e.g. D-Dimer and C-reactive protein) are those that seem more frequently associated with higher risk of developing severe/critical COVID-19 illness [9]. Another important aspect that has now noticeably emerged, is that patients with COVID-19 frequently display coagulation profiles suggestive of a prothrombotic state, characterized by increased fibrinogen concentration [10] and considerably high levels of D-Dimer [11]. Importantly, it has now been clearly established that COVID-19 not only impair primary [12, 13] and secondary haemostasis [14], but has also an important role in disrupting physiological fibrinolysis [15], thus paving the way to studies aimed at better elucidating the intricate pathogenesis and the interplay of other molecules in the prothrombotic state of COVID-19.

Homocysteine is a sulfur-containing amino acid which is not effectively incorporated into proteins. It is a metabolic intermediate generated when the amino acid methionine is metabolized to homocysteine, and can be excreted in the urine [16]. Homocysteine can be methylated to form methionine or converted through a transsulfuration pathway to cystathionine and then to cysteine. In the methylation pathway, vitamin B12, folate and the enzyme methylenetetrahydrofolate reductase (MTHFR) are needed, so that deficit or severe deficiencies of these vitamins can lead to homocysteine accumulation in the blood, especially in those bearing specific mutations in the MTHFR gene [17]. As concerns the transsulfuration pathway, vitamin B6 and the enzyme cystathionine-β-synthase (CBS) are needed. Renal function is another factor that influences homocysteine levels [18]. Hyperhomocysteinemia is typically defined as the presence of an abnormally elevated concentration of plasma total homocysteine [19]. Although in certain cases the degree of hyperhomocysteinemia has been defined as “moderate/mild” “intermediate” or “severe”, no agreement has been reached on the thresholds that should define such limits. With a “normal” concentration typically ranging between 5–15 μmol/L, mild, intermediate and severe hyperhomocysteinemia have been historically defined by Donald W. Jacobsen as plasma values ranging between 15–25 μmol/L, 25–50 μmol/L and >50 μmol/L, respectively [20].

It is known that very high plasma homocysteine values observed in homocystinuria due to CBS deficiency can lead to cardiovascular disease [21]. Conversely, the association between moderately elevated homocysteine values and cardiovascular complications remains more controversial. Refsum and colleagues explored this association in a population of over 18,000 subjects [22], concluding that hyperhomocysteinemia was associated with the risk of hospitalization for cardiovascular diseases in a concentration-dependent manner, but became more significant in the elderly (i.e., after 65 years of age). van der Meer and colleagues also found that elevated homocysteine levels were associated with venous thrombosis [23].

To this end, despite that the association between homocysteine and cardiovascular diseases remains partially unresolved as it has not been definitively proven whether this metabolite is a an active player (i.e., a causal factor) or a simple bystander (e.g., a marker of poor lifestyle or impaired renal function), additional studies have attempted to answer to this question with intervention trials. In the United States and Canada, folic acid fortification of enriched grain products was implemented in the late 1990s [24] and the mean total homocysteine concentration decreased significantly in the general population [25]. Nonetheless, randomized trials have shown that such therapy does not lower the incidence of myocardial infarction [26] or symptomatic venous thromboembolic [27], while only a small benefit was observed for stroke [26]. Therefore, owing to the high burden of thrombosis observed in patients with SARS-CoV-2 infection, especially in those with severe/critical illness, the aim of this article is to provide an updated overview on the possible role played by hyperhomocysteinemia in influencing an unfavorable COVID-19 progression.

Materials and methods

On April 6th, 2022 we carried out an electronic search in Medline (PubMed interface) using the keywords (“COVID-19” OR “SARS-CoV-2”) AND “homocysteine”, between 2019 and the present time, with no language restrictions. The reference list of all documents was reviewed for identifying additional potentially eligible studies. All resulting documents were assessed by title, abstract and full text for observational studies reporting data on homocysteine values in COVID-19 patients with or without severe disease or in non-survivors and survivors. “Severe disease” was defined as imaging progression on chest computed tomography (CT) (increased ground-glass lesions in the underlying involvements or newly occurred lesions beyond underlying involvements) or as significant respiratory distress (respiratory rate upper than 30/min), blood oxygen saturation lower than 93%, ratio between arterial oxygen partial pressure and fraction of inspired O2 (PaO2/FIO2) lower than 300 mmHg, respiratory failure with mechanical ventilation, shock or other organ failures in need of intensive care. Studies fitting the criteria were included in this systematic review. A meta-analysis, using the random effects model to adjust for heterogeneity (calculated with χ² test and I² statistic), was carried out using MetaXL software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia).

Results

A total of 31 studies were initially found, 25 of which were excluded as they did not report homocysteine values.
Three additional studies were eliminated because they did not compare patients with non-severe COVID-19 to patients with severe COVID-19 patients. Thus, three studies, totaling 694 hospitalized COVID-19 patients, were finally included in our systematic review [28–30]. The characteristics of the included studies are summarized in Table 1.

Yang and colleagues [28] carried out chest CT and measured plasma homocysteine at admission in 273 COVID-19 patients. Chest CT was also performed at the 7±2 days during hospital admission, with the purposes of evaluating which patients had worse signs of disease progression on chest CT at the first week. Homocysteine levels were significantly higher in imaging progression patients compared to those found in imaging progression-free (Table 1). In a subsequent study, Ponti and colleagues [29] measured plasma homocysteine in 304 hospitalized COVID-19 patients, reporting that the levels of this substance were significantly higher in non-survivors compared to survivors (Table 1). Finally, Keskin and colleagues [30] measured plasma homocysteine in 117 hospitalized COVID-19 patients. Patients were classified in mild disease group (fever, muscle/joint pain, cough and sore throat, respiratory rate lower than 30/min, blood oxygen saturation higher than 90% in room air) and severe disease group (patients with significant respiratory distress with respiratory rate higher than 30/min, blood oxygen saturation lower than 93%, PaO2/FiO2 lower than 300 mmHg, respiratory failure with mechanical ventilation, shock or other organ failures in need of intensive care units (ICU)).

The results of the meta-analysis are displayed in Figure 1, showing a positive weighted mean difference of 1.75 μmol/L (95%CI, 1.26–2.25 μmol/L; p=0.011) in favor of homocysteine as a risk factor for unfavorable outcome (I², 78%).

Table 1: Homocysteine levels in COVID-19 severe vs. non-severe patients.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Country</th>
<th>Type of study</th>
<th>Sample size</th>
<th>Sex, M/F</th>
<th>Age, years, mean</th>
<th>Homocysteine value, μmol/L, mean</th>
<th>p-Value</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [28]</td>
<td>China</td>
<td>Retrospective</td>
<td>273</td>
<td>134/139</td>
<td>49</td>
<td>9.3±0.2</td>
<td>&lt;0.05</td>
<td>Progression on chest CT</td>
</tr>
<tr>
<td>Ponti et al. [29]</td>
<td>Italy</td>
<td>Retrospective</td>
<td>304</td>
<td>197/107</td>
<td>61</td>
<td>10.8±1.4</td>
<td>&lt;0.05</td>
<td>Mortality</td>
</tr>
<tr>
<td>Keskin et al. [30]</td>
<td>Turkey</td>
<td>Retrospective</td>
<td>117</td>
<td>66/51</td>
<td>63</td>
<td>12.7±0.5</td>
<td>&lt;0.05</td>
<td>Severe disease</td>
</tr>
</tbody>
</table>

NR, not reported; CT, computed tomography. *Values calculated from the natural logarithm. **Severe disease was defined as significant respiratory distress (RR > 30/ min), blood oxygen saturation<93%, arterial oxygen partial pressure/fraction of inspire O2 (PaO2/FiO2) <300 mmHg, respiratory failure with mechanical ventilation, shock or other organ failures in need of intensive care units (ICU).

Figure 1: Weighted mean difference of Ln homocysteine values between COVID-19 patients with and without unfavorable outcome.
Discussion

The results of this systematic literature review evaluated a limited number of studies (n=3) which explored the association between plasma homocysteine and the risk of unfavorable progression of SARS-CoV-2 infection. Nonetheless, some important findings have still emerged. All studied were concordant to show that COVID-19 patients with worse outcomes tended to display higher plasma homocysteine plasma values compared to those with more benign outcomes (Table 1). This would lead us to suggest that, irrespective of its role as active player or bystander, homocysteine could be potentially considered a useful biomarker for stratifying patients at risk of adverse outcome in COVID-19. This should be evaluated in further studies.

Some additional considerations can be made by critically analyzing the outcome of these published studies. In the investigation conducted by Yang and colleagues, the difference in plasma homocysteine between the two groups of patients was found to be statistically significant, though the difference between the two groups was relatively modest [28]. Likewise, Ponti and colleagues found that increasing homocysteine levels were associated with hospital mortality risk, but the odds ratio was also relatively modest (i.e., 1.06), with a homocysteine concentration that only differ by 2.6 μmol between non-survivors and survivors [29]. It is especially important to note that although higher homocysteine levels are associated with cardiovascular events or venous thromboembolism [22, 23], randomized trials have shown that homocysteine-lowering interventions are not effective to lower considerably the incidence of cardiovascular disease [26, 27]. Overall, the differences between the mean values of non-severe vs. severe COVID-19 patients reported in the three articles were always positive, being 15.1% [28], 24.1% [29] and 22.8% [30]), thus generating a positive weight mean difference of around ln(0.09) μmol/L (which translates into approximately ~1.2 μmol/L).

In conclusion, despite the limited evidence that has been garnered so far, increased homocysteine levels appear to be a potentially useful marker for predicting the risk of unfavorable progression in patients with COVID-19.

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References


