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Angiogenic markers as prognostic tools in patients with COVID-19: CRACoV-HHS study

Short title: Angiogenic markers as COVID-19 prognostic tools

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become one of the most prevalent infectious diseases worldwide [1]. Arterial hypertension (HT) was one of the comorbidities initially considered as having influence on the course of COVID-19, however later studies have not proved its detrimental effect [2, 3]. Angiogenesis is impaired in HT and several angiogenic factors have been already used to predict outcomes of hypertension-related acute conditions – such as preeclampsia [4, 5]. Moreover, SARS-CoV2 was considered to have influence on the endothelium [6]. This study aimed to assess the prognostic value of three angiogenic factors (soluble fms-like tyrosine kinase 1 [sFlt-1], angiopoietin 2 [Ang-2], and vascular endothelial growth factor [VEGF]) with regard to the severity of COVID-19.

METHODS

This prospective cohort study was conducted in one academic center. Consecutive patients hospitalized due to COVID-19 were recruited from January 8, 2021 to April 22, 2021. COVID-19 was diagnosed using the reverse transcription polymerase chain reaction method or with antigen test. Demographic and clinical data were gathered on admission. Then, each patient was assigned to severe or non-severe COVID-19 group based on the National Institutes of Health criteria on admission (asymptomatic, mild and moderate illness were classified as non-severe, while severe and critical illness as severe COVID-19) [7]. Serum levels of sFlt-1, Ang-2 and VEGF were measured 5 times – on 1st and 7th hospitalization day, and — 28 days, 180 days and a year after discharge. The concentration of Ang-2 and VEGF were measured by quantitative sandwich enzyme immunoassay technique. The concentration of sFlt-1 was measured by ECLIA on Cobas 8000 analyzer (*Methods* in Supplementary material).

This study is a part of the CRACoV-HHS project broadly investigating COVID-19. The details of CRACoV-HHS have been published before [8]. The study was conducted in accordance with Declaration of Helsinki and was approved by the Jagiellonian University

Ethics Committee, decision number 1072.6120.278.2020. Written informed consent was gathered from participants before inclusion.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 28. Descriptive variables are presented as mean (SD) or median (interquartile range) based on distribution assessed with Shapiro–Wilk's test. The differences between descriptive variables were analyzed with student's *t* test, Mann–Whitney's *U* test or Friedman's rank test as appropriate. A receiver operating curve analysis for prognosis of severe COVID-19 was conducted for each angiogenic factor. The Spearman's rho was calculated for correlation analysis. Categorical variables are presented as number (%) and the differences between groups were assessed with χ^2 test or Fisher's exact test as appropriate. Logistic regression was used to adjust for confounders. Variables found to significantly influence COVID-19 outcomes in previous studies and main outcomes in our study were included into the model. *P*-value <0.05 was considered significant.

RESULTS AND DISCUSSION

There were 229 participants included (median age [interquartile range]: 59 (48–67) years, 35.4% female, 55.7% with HT). 109 patients were assigned to non-severe and 120 patients to severe COVID-19 group. The median body mass index and the prevalence of diabetes mellitus were significantly higher in the severe COVID-19 group (28.65 [25.82–31.83] kg/m^2 vs. 30.03 [26.77–33.22] kg/m^2; *P* = 0.015; 13.3% vs. 24.4%, *P* = 0.036). Detailed baseline characteristics of the study group can be found in Supplementary material (*Table S1*).

In comparison to patients in non-severe group, participants in severe COVID-19 group were in worse clinical condition on admission with lower median blood oxygen saturation, mean systolic and diastolic blood pressure, and higher median respiratory rate (94% [90–96] vs. 88% [85–90]; *P* <0.001; 134.82 mm Hg [16.39] vs. 127.78 mm Hg [16.77]; *P* = 0.002; 82.13 mm Hg [10.4] vs. 78.31 [11.35]; *P* = 0.010; 16 [14–18] vs. 17 [15–20]; *P* = 0.049; respectively). The severe COVID-19 group had significantly higher serum levels of C-reactive protein and lactate dehydrogenase.

Changes in angiogenic factor concentrations showed significant dynamics over time (*P* <0.001). Only VEGF concentrations revealed a pattern, peaking on the 7th hospitalization day: 160.63 (100.85–281.59) pg/ml in the non-severe group and 229.22 (128.02–334.62) pg/ml in the severe group, followed by a systematic decrease thereafter (Supplementary material, *Figure S1*).

Only receiver operating curve analysis of VEGF concentration on admission as a prognostic factor for severe COVID-19 was significant (AUC = 0.687; *P* <0.001). The cut-off value was set at 137.04 pg/ml with 73.8% sensitivity and 56.3% specificity (Supplementary material, *Figure S2*). There was a significant negative correlation between blood oxygen saturation and VEGF and sFlt-1 concentrations on admission (rho = –0.289; *P* <0.001; rho = –0.216; *P* = 0.017, respectively), while there was a significant positive correlation between Ang-2 concentration on 7th hospitalization day and blood oxygen saturation (rho=0.287; *P* = 0.002).

VEGF concentration on admission was still a significant predictor of severe COVID-19 after adjusting for confounders in the multiple logistic regression model (OR, 1.005; *P* = 0.003) (Figure 1).

We found that VEGF serum concentration indicates the risk of severe COVID-19. However, Ang-2 and sFlt-1 levels were similar in both groups and could not differentiate severe from non-severe cases.

Comorbidities influence COVID-19 outcomes. Our study found that severe patients had higher body mass index and diabetes prevalence, consistent with previous studies [9, 10].

During COVID-19 angiogenesis is impaired — especially in pulmonary vessels [11]. Therefore, more severe COVID-19 course should be associated with higher concentrations of angiogenic factors. In fact, we found that VEGF concentration is significantly higher in severe COVID-19 group which is in line with previous study but assessing patients in much more serious condition [12].

In our study, Ang-2 concentrations (previously reported in the literature to correlate with a more severe COVID-19 course and mortality [12]) did not differ between the groups. Mohebbi et al. in 2023 investigated Ang-2 and sFlt-1 concentrations in meta-analysis, where they found that both factors are significantly increased in patients with more severe COVID-19 [13]. We hypothesize our different results might be caused by selection bias, as our study did not include patients from the Intensive Care Unit. Therefore, the endothelium might not have been damaged as severely as in patients from previous studies, but a cytokine storm already existed, resulting in a VEGF increase.

We identified only VEGF as a good predictor of severe COVID-19, with AUC = 0.687. VEGF has never been studied in this role before. However, Ang-2 was previously shown to be a good predictor of severe COVID-19 [14].

This is a novel approach to identifying viral infection-predicting factors, as angiogenic factors have not been studied in other coronaviruses before. However, angiogenesis is

stimulated by hypoxia-inducible factor 1α, which is induced by viral infections such as hepatitis C virus or human papillomavirus so it may lead to increased levels of angiogenetic factors [15].

To conclude, considering patients hospitalized due to COVID-19, VEGF concentration upon admission may serve as a useful additional factor for predicting the severity of COVID-19.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None declared.

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Figure 1. Independent predictors of severe course of COVID-19 in multivariable logistic regression analysis (n = 156)

Abbreviations: Ang2, angiopoietin 2; ACE-I, angiotensin-converting-enzyme inhibitors; hsCRP, high-sensitivity C-reactive protein; sFlt1, soluble fms-like tyrosine kinase 1; VEGF, vascular endothelial growth factor