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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Letter to the Editor

Evaluation of the host-response biomarker interferon-γ-induced protein-10 in predicting SARS-CoV-2 infectiousness

Sir,

Polymerase chain reaction (PCR) testing is the gold standard for diagnosis of SARS-CoV-2 infection. However, detection of viral RNA does not necessarily indicate infectious virus [1,2].

Two approaches were established for quarantine practice during the pandemic: first, setting a general timeframe as isolation period; second, aiming to assess infectiousness by measuring viral load [3]. In PCR tests, the cycle threshold (C_T)-value, which indicates the PCR cycles needed for virus detection, inversely relates to viral load. Evidence suggests that contagiousness ceases at C_T-values >30 [4]. For such matters, repeated PCR tests appear uneconomical and might cause unnecessary burden for laboratories. Point-of-care test (POCT) biomarker combinations previously showed potential for diagnosing COVID-19 in the emergency department [5]. Measurements of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon-γ-induced protein-10 (IP-10), and C-reactive protein (CRP), initially developed to distinguish bacterial from viral infections when used within a combinatorial score, have been demonstrated to predict COVID-19 severity [6–8].

Here, we performed a sub-analysis to the previously reported DIRECTOR study to detect possible predictors of infectiousness by evaluating the biomarkers' association to SARS-CoV-2 PCR C_T-values [7,8]. Adult patients presenting to the Saarland University Hospital in Homburg, Germany, were included. Signed informed consent and a positive SARS-CoV-2 PCR were required. All samples (blood, respiratory samples) were acquired repeatedly during routine care. Ethical approval was granted prior to the study (Ärztekammer des Saarlandes, reference number 019/20). Respiratory samples were tested for SARS-CoV-2 via real-time reverse transcription PCR (RT-qPCR). We operationalized infectiousness as PCR C_T-values. For assuming infectiousness, C_T of ≤/>30 was used, based on previous literature [4]. TRAIL, IP-10, and CRP were measured on a MeMed Key® platform (MeMed Diagnostics, Tirat Carmel, Israel). Biomarker levels were paired with patients' C_T-values when they were measured on the same day or, if not available, the day before PCR testing. Only matched pairs were included in the analyses. Variables were reported as the median with interquartile range (IQR) or as the mean with standard deviation (SD). Correlation analyses were performed using Spearman rank test. Receiver operating characteristics (ROC) curves were generated to assess the performance of the biomarkers' prediction on infectiousness including all possible decision thresholds. In addition, groups were compared by Mann–Whitney *U*-test. For analyses, R Studio (Version 1.3.1093) was used. Statistical significance was set at $P < 0.05$.

The adult DIRECTOR study population comprised 132 COVID-19 patients, in whom the host-response biomarkers were measured 899 times (mean of 6.8 times per patient). Patient characteristics, clinical course and biomarker expression were described in detail previously [7]. Overall, 436 C_T-values from 123 COVID-19 patients (93.18%) were available (mean of 3.54 per patient). In total, 177 C_T-values of 97 patients were matched with host-response biomarkers. The mean of these C_T-values was 28.98 (SD: 5.36).

IP-10 showed a moderate correlation with paired C_T-values ($r = -0.404$; $P < 0.0001$), with a mean level of 804.6 pg/mL (SD: 995.3). TRAIL ($r = -0.108$; $P = 0.153$) yielded no correlation, whereas CRP displayed a weak correlation with concurrent C_T-values ($r = -0.150$; $P = 0.046$). The mean of CRP measurements was 81.44 mg/L (SD: 69.99). When assessing paired values for patients who remained in the normal care unit (NCU) separately ($N = 123$), we found a stronger correlation for IP-10 ($r = -0.412$; $P < 0.0001$; Figure 1A) and CRP ($r = -0.191$; $P = 0.034$). When dividing pairs by C_T-values ≤30 ($N = 91$) and >30 ($N = 86$), IP-10 levels showed a significant difference in group comparisons ($P < 0.0001$). In the group assumed to be 'infectious' (C_T ≤30), IP-10 levels yielded a median of 663 pg/mL (IQR: 1166), whereas IP-10 measurements in the 'non-infectious' group (C_T >30) showed a median of 274 pg/mL (IQR: 354.6) (Figure 1B). With an area under the ROC curve (AUC) of 73.1%, IP-10 was superior to CRP (AUC: 57.8%) and TRAIL (AUC: 52.1%) in predicting possible SARS-CoV-2 infectiousness (Figure 1C). An IP-10 decision threshold of 410.4 pg/mL IP-10 reached the best combined performance with a sensitivity of 70.9% and specificity of 67%. A sensitivity and specificity of 100% was reached at a threshold of 3177 pg/mL and 109.3 pg/mL, respectively, whereas an IP-10 level of 904.5 pg/mL yielded a sensitivity of 90.7% (specificity 40.7%).

In this study, we demonstrated a correlation between PCR C_T-values and IP-10 levels in COVID-19 patients. With a threshold of >410 pg/mL, IP-10 predicted possible infectiousness with a sensitivity of 70.9%. IP-10's predictive performance on infectiousness increased in mildly ill patients, possibly since clinical deterioration is triggered by hyperinflammation, causing a confounding variable for IP-10 elevation [7]. As

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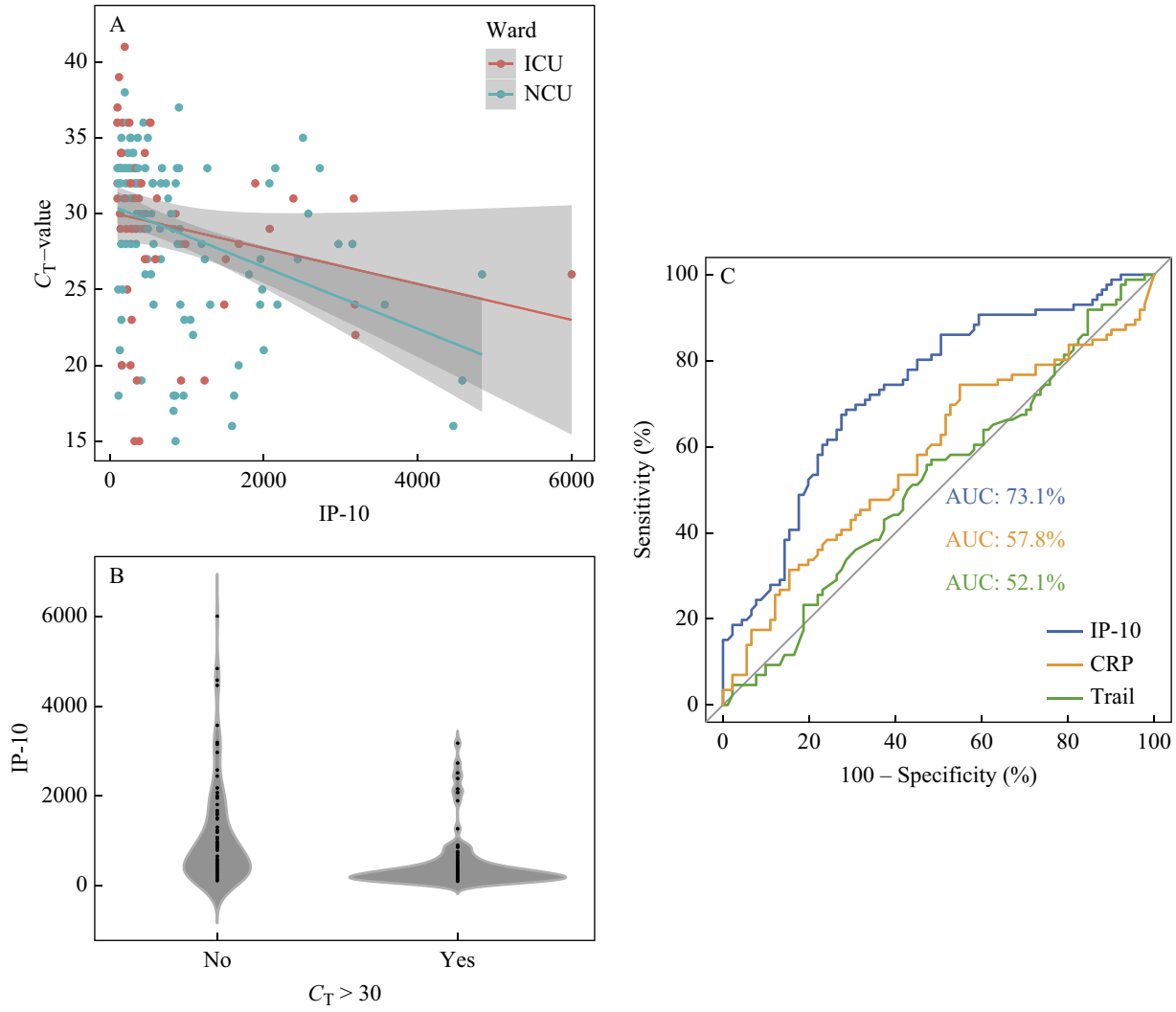

Figure 1. Correlation of interferon-γ-induced protein-10 (IP-10) (pg/mL) in COVID-19 patients to paired cycle threshold (C_T)-values divided by patients in the normal care unit (NCU) and intensive care unit (ICU). Group comparison of COVID-19 patients between paired C_T-values ≤30 and >30. Receiver operating characteristics curves indicating areas under the curve (AUC) for the biomarkers' detection of SARS-CoV-2 infectiousness, as assumed at C_T-values ≤30. CRP, C-reactive protein; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand.

limitations of our study, our pairing of C_T-values with biomarker measurements may have introduced a certain degree of imprecision, and assessing C_T-values for infectiousness is prone to error. Nevertheless, an association of C_T-values with growth of SARS-CoV-2 in cell cultures was previously demonstrated [4]. Furthermore, there is no international standard for calibrating C_T-values, and they are dependent on, for example, method and reagents used [9].

Nevertheless, our findings indicate that POCT measurements of IP-10 could pose an alternative for costly PCR tests in quarantine practice, especially in the outpatient setting, where mild cases are most prevalent. COVID-19 symptoms should be considered alongside the measurements.

Since IP-10 can predict COVID-19 severity, performing measurements could inform on required clinical management as well, improving patient care next to public health.

In children with respiratory tract infections, TRAIL and IP-10 showed significant correlations with different viral loads [7,10]. This suggests that the biomarkers are not limited to SARS-CoV-2. Future studies are needed to externally validate our findings and to evaluate their clinical impact, as well as to assess a direct relation between biomarkers and virus transmission.

In conclusion, biomarkers such as IP-10 represent possible tools in estimating infectiousness of SARS-CoV-2 infection and could overcome the economic limitations of exhaustive PCR testing in quarantine practice.

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Author contributions

S.T. and C.P. conceived the study and its design, had full access to the data, and take responsibility for the integrity

of the data and accuracy of the analysis. Funding acquisition was made by C.P.; S.T., J.E., and C.P. organized and entered data. S.T. and C.P. performed data analyses. All authors contributed to data interpretation. S.T. and C.P. wrote the main draft of the manuscript. All authors contributed to the final drafting of the manuscript.

Conflict of interest statement
None declared.

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Ethics approval statement
This study was approved by the ethics committee of the Ärztekammer des Saarlandes (reference number 019/20).

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