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.

[3]Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich; [4]Institute of Experimental Immunology, University of Zurich, Zurich; [5]Department of Thoracic Surgery, University Hospital Zurich, Zurich; [6]Biontech Innovative Manufacturing Services, Idar-Oberstein, Germany; [7]Department of Immunology, University Hospital Zurich, Zurich; [8]Faculty of Medicine, University of Zurich, Zurich; [9]Faculty of Medicine, University of Basel, Basel; [10]Onkozentrum Zürich, Swiss Tumor Immunology Institute, Zurich, Switzerland
(*E-mail: alessandra.curioni@usz.ch).

†Equal contributions.

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DISCLOSURE

The authors have declared no conflicts of interest.

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COVID-19-associated pancytopenia can be self-limiting and does not necessarily warrant bone marrow biopsy for the purposes of SARS-CoV-2 diagnostics

We read with great interest the report by Issa et al.[1] describing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated pancytopenia. Infection with SARS-CoV-2 and the resulting Corona virus disease (COVID-19) can affect virtually any organ of the human body, including the bone marrow. We report a case of pancytopenia associated with COVID-19 infection. While this case shares similarities with that reported previously,[1] there are also differences which merit consideration.

A 49-year-old man was diagnosed in 2014 with follicular lymphoma grade 3A, stage IVA (Lugano) with involvement of the bone marrow. The patient had normal blood work and was followed without treatment. In 2017, transformation to diffuse large B-cell lymphoma, stage IVB, was diagnosed on bone marrow biopsy and he received immunochemotherapy. End-of-treatment positron emission tomography—computed tomography showed mixed response and bone marrow biopsy found no lymphoma cells, but grade 3 fibrosis.

Relapse of diffuse large B-cell lymphoma was confirmed in April 2019. Salvage chemotherapy followed by high-dose chemotherapy with autologous stem cell support resulted in complete remission. Bone marrow biopsy before autologous stem cell support contained no lymphoma or fibrosis. In October 2019 and January 2020, blood work was normal and a computed tomography scan in January 2020 still showed a complete remission.

In April 2020, the patient was admitted with fever and symptoms of an upper respiratory tract infection. Throat swab was positive for COVID-19. He was discharged after a few days, only to be admitted again 10 days later with continuous fever and cough.

The blood work at the time of second hospitalization showed, for the first time, a low platelet count (Figure 1). He was still positive for COVID-19 by tracheal suction. With suspicion of immune thrombocytopenia, which has previously been associated with COVID-19,[2] the patient was started on immunoglobulin infusions, but never received steroids. He had normal platelets in late January, but then

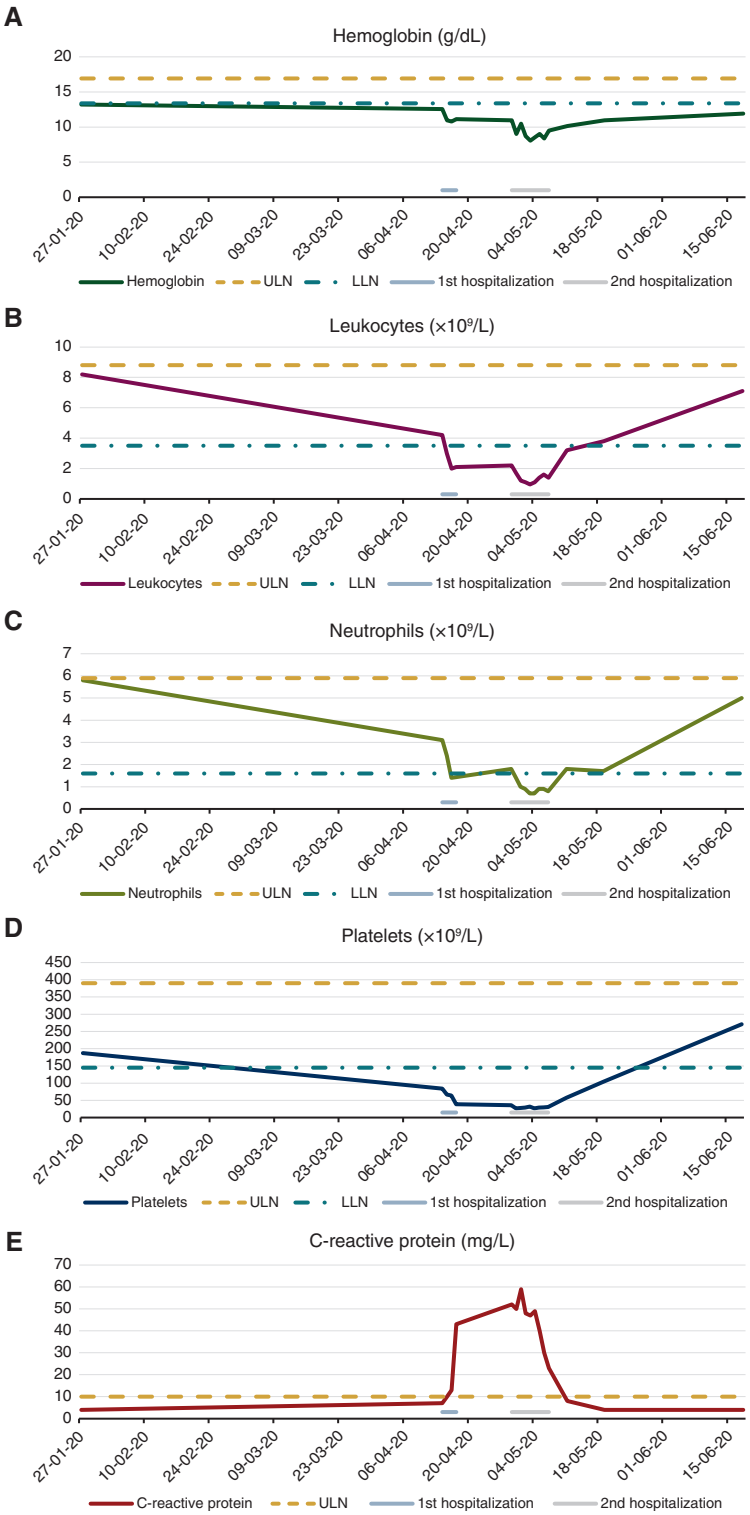

Figure 1. Temporal evolution of (A) hemoglobin, (B) leukocyte count, (C) neutrophil count, (D) platelets and (E) C-reactive protein.
Upper limit of normal (ULN) and lower limit of normal (LLN) according to local laboratory standards are indicated with the dotted lines. Periods of hospitalization are marked with the gray horizontal lines.

the platelet count steadily declined from the middle of April, coinciding with COVID-19 symptoms. Both neutrophil counts and hemoglobin decreased as well (Figure 1). In addition to immunoglobulin, he was treated with meropenem on suspicion of bacterial superinfection, but despite repeated microbiological examination of blood, urine, mouth wash and tracheal secretions, no other microbiological agents were found apart from SARS-CoV-2.

Bone marrow biopsy to investigate the cause of pancytopenia found nonspecific reactive changes, with no sign of

lymphoma, fibrosis or myelodysplasia. RT-PCR analysis of bone marrow aspirate was negative for SARS-CoV-2.

After the patient's infection resolved, his cytopenia improved. At his most recent outpatient visit, platelets, leukocytes and neutrophils had all normalized and only slight anemia remained.

Compared with the case of COVID-19-associated pancytopenia reported by Issa et al.,[1] this case was characterized by a much milder clinical course, an inability to detect COVID-19 in the bone marrow aspirate and a temporally limited duration of pancytopenia matching the duration of infection. As such, pancytopenia in the setting of patients with secondary immunodeficiency with COVID-19 may resemble the type of secondary bone marrow suppression seen in other cases of viral infection.

The patient has consented to the writing of this case report.

D. S. Hersby, T. H. Do, A. O. Gang & T. H. Nielsen*
Department of Hematology,
Herlev and Gentofte Hospital,
Herlev, Denmark
(*E-mail: torsten.holm.nielsen@regionh.dk).

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Prognostic models: clinical impact now within reach

We thank Dr. Halabi[1] for her valuable comments on our article[2] pointing out three main challenges of prognostic models for clinical outcome: (1) generalisability across cancer types, (2) clinical utility and (3) overfitting and availability of orthogonal patient data.

GENERALISABILITY ACROSS CANCER TYPES

We presented the Real wOrld PROgnostic score (ROPRO) as a baseline prognostic score for overall survival (OS), composed of 27 routinely measured clinical parameters. ROPRO is a pan-cancer score which yields consistent performance across 17 different cancer types,[2] (supplementary material). In fact, we set out to develop cancer-specific models; however, since we observed high similarity of parameter estimates across indications, we changed our focus towards a general pan-cancer model. ROPRO may largely perform well because it captures features that are common across different indications and thus measures 'general patient fitness', relevant for OS prognosis.

CLINICAL UTILITY OF PROGNOSTIC SCORES

Assessment of our patients' performance status (PS) to predict survival has always been important for toxicity monitoring, treatment selection and clinical trial eligibility. Some existing tools to determine PS may not be suitable for novel therapies, such as cancer immunotherapy[3] due to their subjective assessment with limited reliability and restricted predictive value in patients with better PS. Tools such as ROPRO may address an unmet need by being more objective and discriminatory. ROPRO is a strong predictor of short-term OS (3—18 months) and can serve as an accompanying biomarker. Long-term prognostic power of ROPRO and validation in large patient cohorts of different ethnicities is needed. We have thus started and encourage testing ROPRO in different patient cohorts for further validation.

The need for dynamic models as pointed out by Halabi[1] is also highly relevant to clinicians. As ROPRO consists of routinely collected clinical parameters, it is possible to compute ROPRO (patient fitness) over time, which may inform patient management, such as switching therapy early in case of inactivity.

OVERFITTING AND AVAILABILITY OF ORTHOGONAL PATIENT DATA

Overfitting refers to choosing a highly parameterised model that fits one particular dataset exceptionally well, but fails to generalise, i.e. reliably predict on new data. To control and test for overfitting, we first used FWER-controlled forward/backward selection and cross-validated LASSO regularisation to penalise model complexity, promoting generalisability over predictive performance. Second, to test for overfitting, we utilised time-stratified data slices from FlatironHealth unavailable at the time of model building and data from 17 clinical studies (Figure 1) showing strong prognostic power with a subtle decrease of the C-index, partially attributed to the fact that patients with an Eastern Cooperative Oncology Group score $>$ 1 are typically excluded from clinical studies.

Additional information regarding the patient's medical history, biomarker and tumour-specific genetics are