

**LETTER TO THE EDITOR**

# The impact of the SARS-CoV-2 pandemic on the ongoing prospective, international, multicentre observational study assessing the preoperative anaemia prevalence in surgical patients (ALICE-trial)

Preoperative anaemia has been defined as an independent risk factor for morbidity and mortality in surgical patients.<sup>1,2</sup> The causes of anaemia are multifactorial, with iron deficiency being the most prominent. Further potential underlying reasons for an inadequate erythropoiesis are lack of vitamin B12 or folate, and bone marrow disease.<sup>3</sup> Anaemia of inflammatory disease is another frequent cause of anaemia and occurs in the context of auto-immune disease, acute and chronic infections and/or cancer.<sup>4</sup> Furthermore, anaemia can be caused by renal dysfunction resulting in a relative deficiency of erythropoietin.

The effectiveness of intravenous iron supplementation to correct iron deficiency anaemia (IDA) has been demonstrated recently.<sup>5,6</sup> However, the PREVENTT trial clearly demonstrated that, if preoperative IV iron supplementation in anaemic patients increases haemoglobin, it does not reduce the frequency of transfusions or the mortality after surgery. Nevertheless, the pragmatic design of the PREVENTT trial precluded extrapolation to specific patients where some factors may have masked the effect of iron supplementation.<sup>7</sup> Indeed, little is known about the proportion of surgical patients who are deficient in vitamin B12 and/or folate and those who suffer from renal anaemia or anaemia of inflammation. The aim of the *Preoperative Anaemia prevalence In surgiCal patiEnts* (ALICE) study is to provide detailed data about the prevalence of preoperative deficiencies in iron, vitamin B12 and/or folate and the presence of underlying renal or chronic diseases in patients undergoing major surgery. The results will facilitate the development of treatment strategies to combat causes of anaemia and to reduce the risk of perioperative complications (NCT03978260).

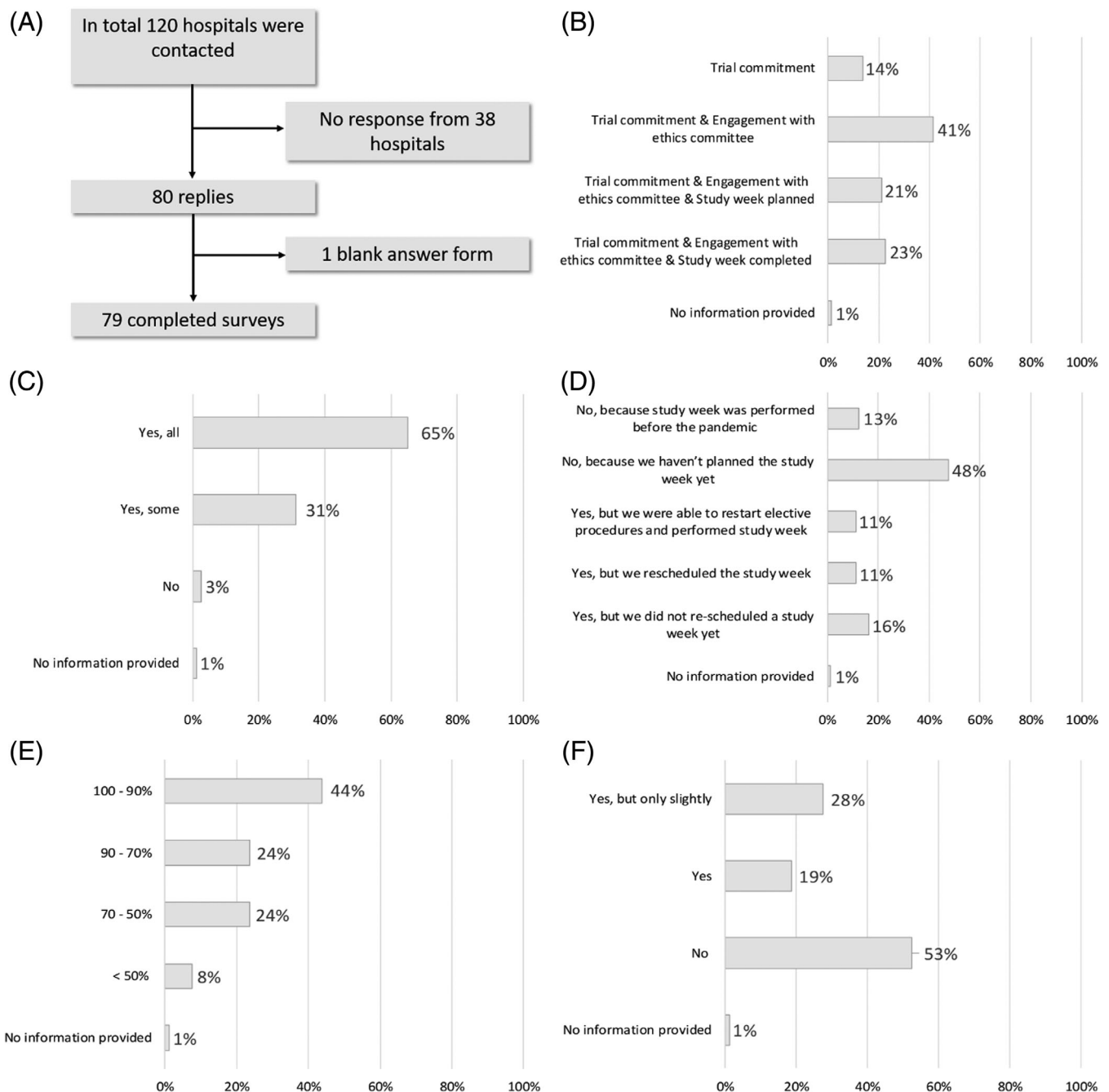
The ALICE-study is an investigator-initiated world-wide collaboration. Within a self-selected study week between 2019 and 2021, participating hospitals recruit patients undergoing major surgery. As many planned surgical procedures were postponed or cancelled globally in order to compensate for the increasing number of SARS-CoV-2 in-hospital patients, the preparation and execution of the ALICE-study had to be paused in many participating centres. The following survey was conducted to assess the status of the ALICE-study and to elucidate if participating hospitals require additional support.

In total, 120 participating hospitals were contacted in August/September 2020 and 79 among them completed the survey

(Figure 1A). Of those centres who responded, 23% ( $n = 18$ ) had already completed and 21% ( $n = 17$ ) planned a study week before the pandemic. Further 41% ( $n = 31$ ) were in the process of finalising ethical approval and paperwork (Figure 1B). During the peak of the pandemic, most planned major procedures were postponed or cancelled in 65% ( $n = 50$ ) of the responding hospitals, whereas some surgeries were reduced in 31% ( $n = 25$ ) of the participating hospitals. Only 3% ( $n = 2$ ) of the centres reported no changes in the daily surgical procedures (Figure 1C). Overall, the COVID-19 pandemic delayed milestones such as site activation or enrolment.

After the peak of the first SARS-CoV-2-wave in their country 11% ( $n = 10$ ) of the participating centres resumed planned procedures and conducted the study week. In addition, 11% ( $n = 9$ ) of participating centres rescheduled the study week. Because of the continuous pandemic, 16% ( $n = 13$ ) did not reschedule a study week (Figure 1D). Approximately three months after the first wave of SARS-CoV-2, 44% ( $n = 33$ ) of the participating hospitals have returned to the status quo regarding their surgical routine. On average half of the hospitals are performing 70–90% ( $n = 19$ ) or 50–70% ( $n = 17$ ) of surgeries compared to before the pandemic and only 8% ( $n = 6$ ) are conducting less than 50% interventions.

Over half of the participating centres (54%,  $n = 42$ ) believe that the SARS-CoV-2 pandemic will not influence the study results. Nearly one third ( $n = 22$ ) assume that it might influence the outcome, but only slightly. Less than 20% ( $n = 13$ ) expect that it will affect the results. Since the SARS-CoV-2 outbreak, the percentage of emergency surgical procedures increased in many hospitals. Depending on the time of patient recruitment, the estimation of the overall prevalence of anaemia might be affected since emergency cases are more frequently anaemic than elective cases.<sup>8</sup> Furthermore, surgical outcome including length of stay and allogenic blood transfusion rate might be altered. The results of this survey indicate that the SARS-CoV-2 pandemic interrupted standard clinical practice. As many preoperative anaemia clinics are closed, diagnosis and treatment of IDA might be impeded,<sup>9</sup> particularly in institutions performing mostly elective surgery such as orthopaedic clinics, where the shift towards urgent/emergent surgery might have been more significant. Elective surgery is also more likely to benefit from pre-operative anaemia detection and treatment programs, whose activity has been disrupted



**FIGURE 1** The effect of the SARS-CoV-2 pandemic on the ALICE-study. (A) Flow chart, (B) Which milestone(s) has/have been achieved? (C) During the peak of SARS-CoV-2 pandemic, were elective major procedures postponed/cancelled at your hospital? (D) During the SARS-CoV-2 pandemic, was the planned study week postponed? (E) After the first wave of SARS-CoV-2 pandemic and going back to ‘routine’, do you perform the same amount of surgeries as before the pandemic? (F) Do you believe the SARS-CoV-2 pandemic will influence the study results?

by the pandemic. In addition, oncological patients have been heavily affected by postponed surgeries leading to further tumour growth. These patients often require intravenous iron supplementation and may need to be analysed separately.

Clinical research has been greatly affected by the medical emergency and scientific activities being either suspended or shifted towards SARS-CoV-2-oriented projects. Since only institutions who had already expressed an interest in the Alice-study were

contacted for this survey, but recruitment was still ongoing when the pandemic rose, we do not know how many centres might have been discouraged from embarking on a new research project altogether.

The ALICE study provides a unique possibility to evaluate the causes of preoperative anaemia, facilitating treatment strategies and thereby improving patient safety and surgical outcome, even in challenging times of the pandemic.

**CONFLICT OF INTEREST**

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**AUTHOR CONTRIBUTIONS**

LJ, DMB, EB, SL, PM, MP, RR, MR, DRS, CS, KZ, SC and PM wrote the manuscript with input from the ALICE-Study-Group. LJ, DMB, EB, SL, PM, MP, RR, MR, DRS, CS, KZ, SC and PM designed survey. LJ, SC, KZ and PM analysed data and wrote first draft of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.