To the Editor:

The systematic review and meta-analysis on timing of cranioplasty (CP) and differences on neurological outcome by Malcolm et al[1] updates their previous study from 2016,[2] and follows another relatively recent one written by Xu et al in 2015[3] on the complications and recovery of neurological function in patients treated with early or late CP following decompressive craniectomy (DC). When comparing those studies, we have noticed that not much has changed in the last 3 years. This also reflects our still limited understanding of the biological impact of DC and CP in terms of cerebral blood flow alterations, cerebrospinal fluid hydrodynamics, and brain metabolism; hence the open questions related to their functional and behavioral drawbacks.[4-10] Hopefully, the attention of the scientific community is vivid as demonstrated by the average 80+ articles indexed on PubMed each year on these topics: this outlines the increased awareness that the interval between DC and CP, the shape and materials used for CP could all act as modifiable factors potentially influencing the clinical outcome.[11-13]

Of note, the 2 groups propose a different definition of early and late CP (<3 months vs <6 months; and 3-6 months vs >6 months, respectively); it is therefore not surprising that, despite roughly covering the same decade, only 2 surgical series were considered by both. [14,15] As a result of these initial differences, the authors focused on slightly different aspects revolving around CP and somehow reached different conclusions. Both groups agree that early and late CP carry similar risks of overall surgical complications (namely: infection rate, intracranial hematoma, subdural collections); although Xu et al[3] suggest that early CP might bear an increased risk of hydrocephalus. As for Malcolm et al,[1] it would have been interesting to enrich their meta-analysis with more insights on this issue, but on this occasion unveiling how shunting influences outcome in early and late CP was beyond the scope of their study.[16] On the other hand, both groups pinpointed that CP at any time is associated with significant neurological improvement; whereas the superiority of early CP is mostly strengthened by the 2 surgical series they have in common, which represent also those with longer follow ups (5-6 months), thus raising concerns that shorter outcome could have biased the results in other series.[14,15]

Malcolm et al[1] certainly deserve praise for attempting a more in depth analysis on functional outcome following CP, and suggesting Barthel index (BI) as the most sensitive tool for discriminating the optimal time for this procedure. Their task was difficult, as they claim, due to

the heterogeneity of the literature in terms of reason for DC, type of CP, cohort subgroups, and outcome measures reported. As shown by the funnel plot that we have reconstructed (MedCalc Version 18.2.1, MedCalc Software, Ostend, Belgium) with data from the 5 studies reporting BI as outcome measure (see Figure 1), Malcolm et al[1] based their conclusion on very diverse (Cochran's Q test for heterogeneity: 33.07) and inconsistent raw data (I^2 inconsistency index: 87.91%).[7,14,15,17,18] A funnel test is less accurate whenever based on a limited number of studies, as in this case, nonetheless we herein propose this additional analysis because it provides the readers with a strong visual impact, and a fairly accurate estimate of the external validity of the results discussed.

The point here is that we are still far away from addressing the initial research question regarding the optimal timing for CP. To have greater chances to do so in the future we should perhaps ask ourselves which management protocols should be homogenized, as well as which areas of research would deserve investments the most.[19]

An awareness that many different factors, not only clinical but also organizational, come into play in the decision making process regarding the timing for CP, would optimize the inclusion criteria and protocols for future trials. In the last 15 years, for instance, the number of certified tissue banks has steadily increased; this trend was paralleled by a reduced use of cryopreservation or subcutaneous abdominal implantation of autologous bone flap after DC.[20] Differences in healthcare systems, along with the abovementioned changes in clinical practice, simply reflect that management strategies are evolving over time and so is our approach to CP: bone flaps are more and more discarded after initial DC with a tendency to offer custom made bone flaps to our patients, should they survive the acute phase of the underlying pathology.[21] At times, these aspects could all result in a procrastination of the intervention date.

What is needed then is a collegiate effort to foster both large randomized controlled trials (RCT) and mechanistic studies. RCT could actually overcome the low evidence of a superiority of early CP (Class IIb, Level C) deriving from non-randomized retrospective cohort studies; it is therefore disappointing to interrogate international clinical trials databases (clinicaltrial.gov; eudract.ema.europa.eu; ukctg.nihr.ac.uk) and find only 2 prospective RCT on timing of CP, currently ongoing in Germany (DRKS-ID: DRKS00007931) and China (CTG-ID: NCT03222297).[22,23]

Reaching a consensus on the definition of early and late CP would certainly help in reducing the existing confusion; furthermore consistency in terms of outcome measures reported would enhance the inferences of clinical research on nationals and international guidelines.[24] Going forward, our specialty will benefit from an international validation of objective measures able to guide clinicians in choosing the best timing for CP. The Brain Sunken Ratio is a valid attempt to propose an objective measure other than the time interval between the DC and CP to enhance neurological outcome; in a preliminary study this radiological ratio resulted statistically significant in predicting complications rate and overall outcome.[25] Noteworthy, the investigators of a recently concluded French RCT (CTG-ID: NCT01113645) studying the impact of cranioplasty on cerebral hemodynamic and blood flow suggested that CT perfusion could be a viable tool in the decision making process for CP.[26]

A systematic review is successful whenever it identifies knowledge gaps; hence we believe that the best path toward optimization of timing for CP surgery and consequent quality care improvement should pass through adoption of unified definitions, consistent outcome measures, and validation of predicting biomarkers/biosignatures.[19,21-24,27]

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FIGURE LEGEND

Figure 1: Tests for heterogeneity, Forest plot and funnel plot (software used: MedCalc Version 18.2.1) realized by considering the standardized mean differences (SMD) in Barthel Index (BI) from some of the studies included by Malcolm et al[1] in their systematic review. BI was the performance scale used in 5 out of 8 of the studies reviewed. [7,14,15,17,18] The classical measure of heterogeneity is Cochran's Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies; whereas the I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. Theoretically, it can be assumed that studies with high precision included in any given systematic review when plotted in a funnel triangle will tend to the height of the triangle (average value), whereas studies with low precision will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Whereas the Forest plot indicates that patients undergoing early CP showed significant improvement in BI (a measure advocated as the most sensitive tool for discriminating the optimal time for CP), the additional statistics reveals that most of the studies included fall outside the funnel triangle highlighting the limited inferences that can be obtained from their comparison.

Figure 1

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