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Risk factors for necrotizing enterocolitis at a neonatal intensive care unit

Mr. Editor:

I have read with interest the article by Ongun et al.[1] *"Developing necrotizing enterocolitis: retrospective analysis of 1428 preterm infants in a level III neonatal intensive care unit over a four-year period"*. I will not pass up the opportunity to thank the authors of this published work, since the aim was to obtain information about this pathology in premature newborns and its possible association with risk factors.

When evaluating this scientific publication, I have noticed some aspects that could have intervened in the results. Thus, it should be noted that when compared with other studies that have the same line of study, the sample size is small and is only limited to a single neonatal intensive care unit. Another important point is the fact that the data that were taken into account to obtain reliable results are retrospective. This, in a way, tends to give limited precision when one wants to prove that the results are really true and that there really is an association between a dependent variable with an independent.[2]

When doing a bibliographic search, I was able to see another publication in which NEC in premature newborns is also taken as a central theme. In the study by T. Qian et al.[3] the same method of analysis was used, the retrospective one, with the inclusion of all cases of NEC in neonates with a low birth weight. In this case, the data could be considered more reliable because 95 hospitals were included, therefore, it is easier to obtain more cases for a better analysis of the risk factors that are associated with the appearance of NEC. A point of comparison is that this cohort was more detailed in identifying its respective stages in each case of NEC. This is helpful to be able to collect data and identify other risk factors that may explain the appearance of NEC according to the phase in which it is located.

Finally, in the article by Ongun et al. it is mentioned that there are no previous studies on the relationship between cesarean section and the appearance of NEC, suggesting that cesarean section would be a risk factor for this pathology. However, in the article by T. Qian et al.[3] showed that NEC is related to infections that progress to sepsis and that it is not necessarily related to cesarean section, since the onset of the infectious process could occur before, during or after NEC.

Another study that I consider important to mention is that of Qi Lu et al.,[4] a retrospective case-control study. One of its objectives was to identify whether the presence of neonatal sepsis was related to the appearance of NEC, which was briefly described as the fact that there was indeed a correlation However, in the article by Ongun et al., it is mentioned that this data was collected in the group of patients, but no explanation was given for this variable in the Discussion of the results.

Despite having these observations, points have been seen in favor due to the controlled nature of this study on the groups of patients. However, data on newborn daily intakes and feeding intervals were not taken into account, just as mentioned within the limitations, which could be expanded a little further. It is important to take into account in this section of the article the fact that data was taken from a single center, which clearly decreases the reliability of the results. In my opinion, this work has the potential to be able to identify the risk factors for the progression from NEC to intestinal perforation, which can be complemented with other research that seeks the same purpose, but taking into account the limitations that should be avoided for a better use of the results that would be obtained.

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Dear editor,

The authors read Dr. Barrera's letter with great interest and express their sincere gratitude to her criticism regarding the publication '*Developing*

necrotizing enterocolitis: retrospective analysis of 1428 preterm infants at a level-III neonatal intensive care unit over a four years period'.

The author shared her concern regarding nature of the study which was a single-center, retrospective cohort that was conducted in preterm infants with gestational age ≤ 37 weeks. She speculates whether this single center study leads to small sample size with risk of bias due to retrospective design, hence the results cannot be reliable. Despite her concern, one should figure out nature of necrotizing enterocolitis (NEC) publications on preterm neonates. There have been vast majority of NEC studies from retrospective single center ones to multicenter cohorts or meta-analysis evaluating global incidence,[1] different preexisting conditions,[2-4] mortality risk factors based on birthweight categories,[5] preventive strategies[6-8] and approach to surgical interventions in case of intestinal perforation.[9] By the time of this publication, several risk factors have been identified in the progression of NEC, but very few had focused on risk factors and conditions ultimately proceeding to intestinal perforation (from feeding intolerance to intestinal perforation). As mentioned in the methods section, the current NICU is one of the largest and highly referral centers among Mediterranean region of Turkey, the annual admission rates are 850-1100 newborns per year. Moreover, multidisciplinary approach under the supervision of board-certified neonatologists and pediatric subspecialties in addition to surgical consultants has led this NICU to become one of the highest referral centers; approximately half of the admissions consist of postnatal-transfers. Hence, health-care providers of this NICU deliver advanced neonatal care to a highly variable group of neonates that makes the study population a heterogenous group of patients. So by retrospectively observing this heterogenous group, the authors aimed to identify the ones who only suffer mild NEC in the form of feeding intolerance and not proceed to perforation or the ones who suffered severe forms of the disease. The results have demonstrated *i)* mode of conception and CS delivery were associated with acquiring NEC, *ii)* timing of first enteral feeding and hemodynamically-significant PDA were predisposing factors for NEC, while low 5-min Apgar score was the single independent predictor for intestinal perforation. We believe the results could guide health-care providers delivering neonatal care in this manner and contribute to literature.

Dr. Barrera also mentioned her concern regarding the association between cesarean section (CS) and NEC by quoiting the work of Qian et al.,[5] who hypothesized NEC is related to infections that progress to sepsis and not necessarily related to CS delivery, since the onset of the infectious process could occur before, during or after NEC. We oppose this hypothesis, because recent research also demonstrated the role of intestinal immaturity and microbial dysbiosis in NEC pathophysiology. Lack of colonization with vaginal flora in CS delivery has been proposed to trigger microbial dysbiosis in preterm neonates and the authors of the present publication have discussed this point in detail. Besides association between CS delivery and NEC have been shown in a recent study from the Israel Neonatal Network.[10]

Dr. Barrera's final critics was the absence of information regarding sepsis on discussion section. We, as the authors of this publications intentionally disregarded the well-known issue of sepsis due to limitation on the word count of the journal.

In conclusion, we appreciate Dr. Barrera's criticism regarding our publication hoping the answers would satisfy the author's concern.

Thank you.

On behalf of other authors,
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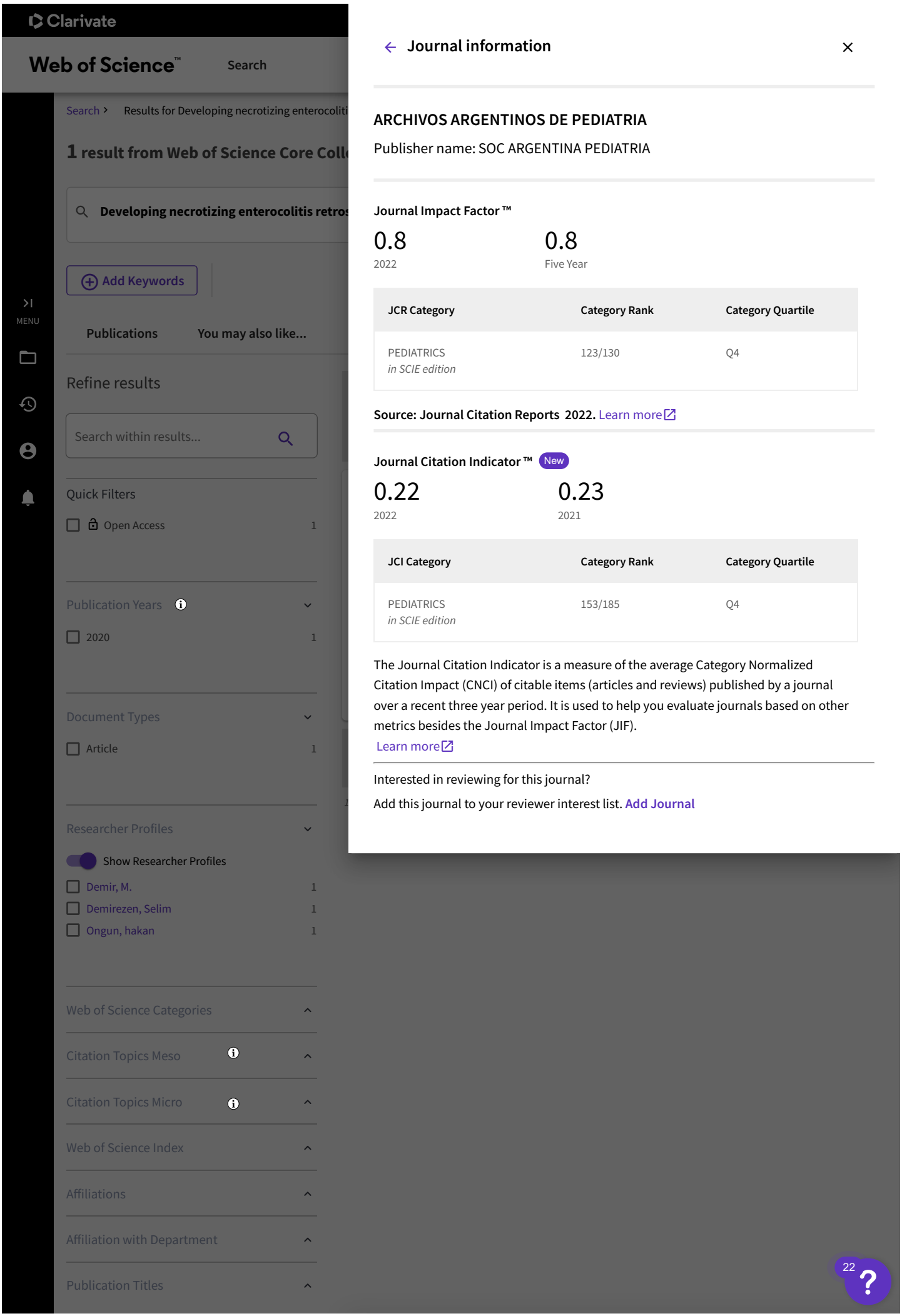
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