Conflict of interest

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A scoring system for biliary atresia: Is this the right one?

To the Editor:

We read with interest the recent article by El-Guindi *et al.* [1].

An effective bedside diagnostic score for biliary atresia (BA) in cholestatic infants, despite decades of clinical experience, is still lacking, and none of the few proposed in the past achieved a widespread application in clinical practice [2–4]. The task is tough; the perfect score should fulfill two conflicting requirements. Despite the great clinical heterogeneity, a near 100% sensitivity is mandatory because of the time-dependent surgical treatment. On the other hand, invasive procedures, such as intraoperative cholangiography or liver biopsy, should be avoided as much as possible in very small children.

Starting from state-of-the-art knowledge about all previously reported signs of BA, El-Guindi *et al.* formulated a new twelve-point diagnostic score using a smart statistical approach. Subsequent validation on a cohort of 75 consecutive patients showed an overall high diagnostic accuracy of 98% (sensitivity 100%, specificity 97.6%). Because of such relevant results, we aimed to challenge this scoring system with our historical series of cholestatic newborns and compare results with those of our current diagnostic protocol.

From January 2009, 64 patients were referred for neonatal cholestasis. After initial assessment, including clinical evaluation, ultrasound and targeted laboratory and/or radiological test to rule out other definite diagnosis, 16 of them underwent liver biopsy, 2 endoscopic retrograde cholangio-pancreatography, and 18 intraoperative cholangiography. Sixteen newborns received the diagnosis of BA and underwent Kasai procedure at a median age of 62 days (range 34–128 days), with a median delay of 6 days from the first evaluation (range 1–47 days). Only three patients were not correctly diagnosed at the end of the first evaluation. One patient with BA was addressed to intraoperative cholangiography with a delay of 47 days because cholestasis was initially ascribed to the concomitant Hypothyroidism. Conversely, two newborns, which later received a diagnosis of neonatal sclerosing cholangitis and non-syndromic ductal paucity, respectively, underwent intraoperative cholangiography.

Liver histology was available for review in 27 cases, 16 from needle biopsy and 11 from surgical biopsy. In this series of 27 patients, we retrospectively calculated the diagnostic score of El-Guindi *et al.* at the time of first evaluation. Mean age at first evaluation of the 27 infants was 60.4 days (range 29–122 days), 16 children had BA and 11 another cause of neonatal cholestasis (3 transient neonatal cholestasis, 1 cystic fibrosis, 1 neonatal sclerosing cholangitis, 1 hypothyroidism, 2 non-syndromic ductopenia, 1 mitochondrial depletion syndrome, 1 Niemann-Pick type C, 1 biliary acids synthesis defect).

Clinical, histological and laboratory items were extracted from medical records. A single radiologist (MPM) with specific experience in the field [5], unaware of final diagnosis, reviewed all recorded ultrasound examinations, performed after six hours of fasting, and calculated radiological items. Among them, only gallbladder contractility was not possible to be evaluated from the recorded images. This item was estimated comparing the first examination, performed after fasting, with other tests performed randomly in the following days. At least one follow-up ultrasound was available for all patients. Prevalence of single items of the score is showed in Table 1. Global sensitivity was 31%

Table 1. Prevalence of clinical, histological and laboratory items in relation to the diagnostic score.

	BA (n = 16)	Non-BA (n = 11)
Clay stool	8 (50%)	1 (9%)
Triangular cord	2 (12.5%)	0
Contractile gallbladder	2 (12.5%)	5 (45.4%)
GL >20.5 mm	0	3 (27 %)
HAD >2.05 mm	4 (25%)	2 (18.2%)
HAD/PVD >0.445 mm	8 (50%)	5 (45.4%)
Hepatic subcapsular flow	1 (6%)	0
gGT >286	14 (87.5%)	6 (54.5 %)
PLT >349,000	11 (68.7%)	5 (45.4%)
DP	16 (100%)	6 (54.5 %)
BP	13 (81.2%)	3 (27 %)
GC	8 (50%)	3 (27 %)

GL, gallbladder length; HAD, hepatic artery diameter; PVD, portal vein diameter; gGT, gamma glutamyl transpeptidase; PLT, platelets; DP, ductular proliferation; BP, bile plugs; GC, giant cells.

(5/16), specificity 90.9% (10/11), positive predictive values was 0.81 and negative predictive values 0.47. Overall diagnostic accuracy resulted 0.55.

Reasons for such disappointing results might be numerous. First, the retrospective nature of this study is a major confounding factor. A large, multicentric, prospectic study is needed to validate this score. On the other hand, we believe that our group of patients is quite different than the one used by authors to validate the score. Our patients belong to a highly selected subset of cholestatic infants, addressed even from reference centers for invasive investigation. This new scoring system seems to work poorly in this clinical setting, but the paradox is that an effective score is typically needed in such kind of patients.

Children with a various combination of cholic stools, mild cholestasis, known risk factors for transient cholestasis, normal GGT activity and other features not suggestive of BA might be, in most cases, effectively managed without the need of liver histology as our results suggest. The overall performance of our current protocol (3 diagnostic errors out of 64 cases), indeed, is similar to that of this new scoring system, as claimed in the paper. However, 48 liver biopsies were spared. Moreover, even a large, prospective, collaborative study must include some kind of selection criteria because it might not be ethical to propose a liver biopsy to all children with "direct hyperbilirubinemia", as stated in the paper, without further details.

In conclusion, waiting for results of prospective studies, we believe that we are still waiting for an efficacious and practical clinical score for BA.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "A scoring system for biliary atresia: Is this the right one?"

To the Editor:
We appreciate the interest of Sciveres and colleagues in our recent study [1] and we would like to respond to their letter and help them answer the question they raised. Looking thoroughly into their retrospective study, many limitations can be easily pointed out and may account for their disappointment and poor results. First, the retrospective nature of the study was not the optimal approach for the validation of the biliary atresia (BA) score. Second, the small number of patients (n = 27) in their study carries a very low statistical power of 28.2% at an alpha of 0.05, 2-tailed with 95% CI. This intensifies the need for validation of the BA score on a sample size larger than the one in the original article (n = 75) by El-Guindi *et al.*, as we already suggested. Third, the historical data they collected were not pre-designed to evaluate the score parameters beforehand. For example, the gallbladder length before and after