



A novel use of the comprehensive complication index in perihilar cholangiocarcinoma surgery

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It is well known that radical intent surgery is, as of today, the only curative treatment available for perihilar cholangiocarcinoma (pCCA); the standard surgical procedure includes major hepatectomy with caudate lobe resection and extrahepatic bile duct resection (1). A recent paper set the benchmark values for pCCA surgery: in this paper, acceptable benchmark values for morbidity, severe morbidity, and 90-day mortality were $\leq 87\%$, $\leq 70\%$, and $\leq 13\%$ respectively. This confirms how, even in expert hands, this type of resection is still burdened by high morbidity and mortality (2,3), and it has been proven that every patient undergoing surgery for pCCA has at least one complication, independently of how insignificant it may be (4). In light of these considerations, the proper evaluation and monitoring of postoperative complications become of the utmost importance; the most used system is the Clavien-Dindo classification (CDC) (5), while other authors preferred to create specific grading systems for different complications, such as posthepatectomy liver failure (PHLF) or bile leak (6,7). All these systems, however, lack a “time factor”, failing to encompass the development of overall morbidity, but rather they may be seen as “labeling systems” for postoperative morbidity. That’s why the comprehensive

complication index (CCI), that was designed as a continuous scale from 0 (no complications) to 100 (death) describing the accumulation of morbidity, may allow the longitudinal assessment of morbidity (8).

In their article in *Annals of Surgery* 2023, the authors were able to use CCI to depict the postoperative course of their retrospective cohort of resected pCCA patients as a trajectory of accumulating morbidity (9). Using a statistical tool called group-based trajectory modeling, that automatically identify groups of subjects with significantly different developments of a continuous value over time (i.e., different trajectories) (10), they were able to identify three different postoperative course groups, called mild, moderate and severe, that were associated with different 360-day cumulative mortality risk. They also showed how morbidity tends to increase slowly until postoperative day (POD) 4, then shows an ascension around day 7 and then almost reaching a plateau. Finally, the authors were able to identify three cut-offs for CCI at POD 1, 4, and 7; in particular, the most relevant finding is probably the cut-off of 28.5 at POD 4, which is associated with an 8-fold increase in mortality risk.

This is the first experience reporting a continuous

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sequential recording of CCI, illustrating very well its efficacy in returning a comprehensive image the severity of postoperative course, especially one as often burdened by multiple complications as the one of pCCA patients.

The article by Kawakatsu *et al.* has some undeniable merits:

- ❖ The authors proved how day-by-day CCI evaluation is a better system for postoperative morbidity assessment, encompassing all complications that a patient suffers, but adding a time factor that helps understanding the developing nature of a complicated postoperative course, while other systems are limited to a grading of the severity of single complications, thus failing to reflect the effect of accumulating morbidity (9,11). Moreover, even if the authors themselves argue that in their institution a routine computed tomography (CT) scan is given on POD 7, leading to the discovery and management of complications that may have been hidden till then, it's undeniable how in their vast experience postoperative morbidity grows steadily in the first week after surgery, with a sharp increase around POD 7, and then grows more slowly, almost reaching a plateau, suggesting that the first week after surgery is the most critical period.
- ❖ Cut-offs to predict a severe postoperative course and postoperative mortality results from the analysis conducted; these values may be useful in keeping high the attention level of physicians. Let us take the POD 4 cut-off, set at 28.5, as an example: of course, a single CDC grade IIIb leads to a CCI of 33.7, already exceeding this cut-off, but even two different CDC grade II complications, or five grade I complications and one grade II complication surpass it; and exceeding this cutoff is linked to an 8-fold increase in the risk of mortality. This is, to some extent, the statistical proof of an empirical knowledge often expressed by experienced surgeons, that a patient showing many small, sometimes easy to manage, deviances from a normal postoperative course may be harboring insidious, more severe complications that may lead to a disastrous course or even death. Thus, the day-by-day evaluation of the CCI may help physicians to avoid overlooking accumulating morbidity and discarding it as "mild complications" (9,12).
- ❖ The choice of using group-based trajectory modeling must be praised: this very elegant

statistical method has the substantial merit of detecting different groups of patients with the same developmental trajectory. This way the groups considered in this paper emerged from the data itself instead of being set a priori and then tested, reducing the risk of biases and giving a more data-driven result (10).

Anyway, the authors themselves invite to interpret these results with caution: first of all, while the definitions and protocols reported in this paper are usually internationally validated, some differences in patients' management peculiar of the single institution may have influenced the results. As an example, the authors report a steeper increase of CCI values around POD 7, but they also point out how on this day every patient receives a routine CT scan, that may lead to the diagnosis of otherwise hidden complications such as abdominal fluid collections/abscesses. Moreover, they also report how their aggressive management of these findings may lead to an increase in the grade of morbidity, even if we must agree that it seems to be justified by their results in terms of postoperative mortality. Secondly, this is a cohort from a highly experienced, high volume eastern center, and it is well known the important difference in volume and outcomes between western and eastern centers, especially in terms of morbidity and mortality (13). Given all that, it wouldn't be surprising if the trajectories and cut-offs reported in this paper were not appropriate for a Western cohort. Validation studies are needed to prove that, but we think that this does not change one of the main take home messages of this paper, which is that evaluation of accumulating postoperative morbidity, more than that of severity of morbidity alone, reflects the risk of a severe postoperative course in these very delicate patients.

A final remark must be made: the authors report also preoperative, operative, and pathological characteristics of their patients and it is interesting to notice how very few of these factors seem to be different between the three trajectories of increasing morbidity, even when these factors were known to increase the risk of postoperative morbidity. As an example, no difference was found in terms of extent of resection, liver function (measured through indocyanine green clearance rate) or preoperative cholangitis, all factors linked to increased postoperative morbidity and mortality (14,15). The only differences between all three trajectories were found in terms of operative time and blood losses, which may lead to think that, at least in their cohort, what happens

in the operating rooms is what influences the most the risk of a severe postoperative course. Even so, linking preoperative/operative/pathological features to diverse postoperative courses was not the aim of this paper, so this last consideration should be seen only as food for thought.

Aside from the individuation of trajectories and cut-offs, however useful, the main take home messages of this high-quality paper are as follows: evaluation of accumulating morbidity is as important as, or even more important than, the severity of postoperative morbidity and, in light of that, multiple low-grade complications may have the same, or even worse effect on postoperative course and risk of mortality than single high-grade morbidities. And these notions, that may become empirically clear for the experienced surgeons, find with this paper a formal and easy to understand formulation for trainees and surgeons first approaching this disease.

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