Risk-adjusted analysis of survival variability among hospitals treating biliary malignancy

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Introduction

Biliary tract cancer (BTC) constitutes a heterogeneous group of malignancies arising from the biliary tree and it includes the gallbladder cancer (GC), intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) [1]. In advanced setting, the phaseIII trial ABC-02 led to the approval of Cisplatin plus gemcitabine as first line standard treatment for advancd BTC, achieving a significant improve in overall survival (OS) [2, 3]. In the optic to search new strategies, the use of next generation sequencing has permitted to identify driver genic and

molecular aberrations which could be targeted by new promising molecules, including those against isocitrate dehydrogenase (IDH) 1/2 mutations, fibroblast growth factor receptor (FGFR) fusion, and several pathways like neo-angiogenesis, PI3K/AKT/mTOR pathway, human epidermal growth factor family receptor (EGFRs), thus opening new ways in the treatment of this complex disease. In such a complex scenario, the expertise of the oncologic team derived from high experience and volume of patients and the efficacy of a tumour board constitute significant factors to consider. The role of centralization and of the volume of surgical treatments has already been established in several oncologic disease, thus many guidelines include the recommendation to centralization. In a previous cancer register study conducted on a large sample of patients with CCA, Idrees et al. [4] demonstrated that both centralization of surgery for CCA to high volume hospitals and increased compliance with NCCN guidelines were associated with significant improvements in OS. Regarding the systemic therapies, the role of the variability between institutions and the impact of the team's expertise is less clear. Moreover, in this era of new technologies and of precision medicine, has emerged the role of the physician's confidence in the use of new genomic testing and molecular analysis, which could help in finding new targetable driver [5]. On the other hand, it has to be considered that the role of expertise could be more significant in new therapeutic fields rather than the classic ones, such as those involving classic and relatively known chemotherapy regimes. In such an optic, we performed a large risk-adjusted analysis of patients with BTC treated with systemic therapies from several different institutions, in order to investigate the role of the centre in the survival outcomes of patients treated with first line chemotherapy. For this reason, we decided to consider patients from different Italian institutions with different BTC patients' volume, in order to evaluate with a sophisticated statistical method the impact of the institution on survival outcomes of these patients.

Methods

Patients and clinical data

For this study, we selected 915 consecutive patients with BTC treated for locally advanced (N ¼ 126) or metastatic disease (N ¼ 789) in eleven Italian institutions from February 2002 to April 2018. The institutions involved in the study were: IRCSS Giovanni Paolo II of Bari (N ¼ 64 patients included), Hospital Sant'Orsola Malpighi of Bologna (N ¼ 144 patients included), Hospital of Brindisi (N ¼ 27 patients included), Hospital of Macerata (N ¼ 32 patients included), Istituto Tumori della Romagna IRCSS of Meldola (N ¼ 55 patients included), San Raffaele Hospital of Milan (N ¼ 126 patients included), Hospital Molinette of Turin (N ¼ 61 patients included), Hospitals from Piemonte (N ¼ 221 patients included), University Hospital of Pisa (N ¼ 83 patients included), Campus Biomedico of Rome (N ¼ 33 patients included) and Hospital of Udine (N ¼ 69 patients included). The sample included patients with diagnosis of intra-hepatic cholangiocarcinoma (N ¼ 488), distal cholangiocarcinoma (N ¼ 120), perihilar cholangiocarcinoma (N ¼ 81) and gallbladder carcinoma (N ¼ 226). All patients were reviewed to confirm the pathologic diagnosis of BTC and to restage by performing a chest-abdomen computed tomography (CT) according to the 8th edition 2017 AJCC staging system.

Clinical data including the patients' gender, age, Eastern Cooperative Oncology Group (ECOG) Performance Status; pathological data, including primary tumour location and site of metastasis; and biohumoral data from laboratory tests, including plasma CA 19.9 and CEA levels, hemogram data (neutrophil, lymphocytes, monocytes and eosinophils count), serum bilirubin levels and serum albumin levels, were carefully collected at the baseline, and used for analysis. Patients were treated with one of the following systemic treatments: gemcitabine plus cisplatin (N ¼ 194), gemcitabine in monotherapy (N ¼ 232), gemcitabine plus oxaliplatin (N ¼ 341), modified FOLFOX (N ¼ 38), fluoropyrimidine in monotherapy (N ¼ 34), modified FOLFIRI (N ¼ 5), taxanes (N ¼ 1), FOLFIRINOX (N ¼ 1), antiangiogenic therapies (N ¼ 10), and other treatments (N ¼ 52). For the whole sample, Overall Survival (OS) defined as the interval between the date of the first-line start and the date of death or last follow-up, was evaluated.

Statistical analysis

We firstly sought to determine the heterogeneity of clinical characteristics, consequently these were pooled across centres applying a random-effect model [6]. This returned weighted values as well as I^2 values, a measure of the heterogeneity, interpreted as suggested by Higgins: <25% ¼ low heterogeneity; 25%–50% ¼ medium, 51%–75% ¼ substantial and >75% ¼ considerable [7]. The same was applied for weighted estimation of the primary outcome measure considered.

Table 1. Clinical features of the 915 patients treated for biliary malignancy at 11 hospitals.

Characteristic	Weighted values (95%C.I.)	Heterogeneity (I^2)
Age (years)	65.1 (64.4–65.9)	18.2%
Female	49.2% (46.0–52.4)	0.0%
Malignancy		
Intra-hepatic	57.1% (50.5–65.5)	73.4%
Gallbladder	21.0% (16.1–27.0)	72.8%
Distal	14.1% (10.2–19.2)	71.6%
Peri-hilar	13.2% (8.7–19.6)	79.1%
ECOG – PS		
0	34.5% (24.7–45.8)	86.0%
1	52.9% (41.9–63.7)	88.0%
2	9.7% (6.2–14.9)	67.4%
Haemoglobin (g/dL)	12.4 (12.1–12.7)	86.0%
Total bilirubin (mg/dL)	0.77 (0.62–0.99)	51.3%
NLR (ratio)	3.16 (2.87–3.48)	77.5%
CEA (mg/L)	5.96 (4.23–8.40)	90.5%
CA19-9 (U/mL)	159 (121–209)	64.0%
Metastatic disease		
Peritoneal	11.6% (7.6–17.3)	49.4%
Lung	10.2% (0.7–14.6)	47.6%
Bone	4.8% (0.3–6.8)	0.0%
Gemcitabine + platinum	57.6% (50.4–64.4)	73.3%
Chemotherapy duration (days)	86 (76–96)	67.0%
Mortality within 9 months	52.1% (45.4–58.7)	70.3%

Weighted values and heterogeneity (I^2) derived from meta-analysis of each single centre values through the Der Simonian–Laird estimator.
I^2 statistic can be interpreted as follows: values of <25% = low heterogeneity; 25–50% = medium, 51–75% = substantial and >75% = considerable heterogeneity.
Bilirubin, NLR, CEA, CA19-9 and chemotherapy duration were non-normal distributed, consequently they were pooled after their log-transformation and are here reported after exponential conversion of results.

The relationship between each clinical variable on the main outcome was then investigated through multilevel mixed-effects logistic regression, which predicted what each centre's outcome would have been for a standard patient, removing the predictable effects of differences across centres. Then, risk-standardized outcomes were calculated for each centre involved and confidence intervals calculated with Poisson distribution. Once this adjustment is performed, residual differences in outcomes are assumed to be related to provider quality. No a-priori level of significance was set [8] and single variables were considered for multivariable regressions when their confidence intervals (CI) did not include the 1. Collinearity was verified through variance inflation factor (VIF) evaluation.

Analyses were performed using R-Project 3.2.5 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Results

Weighted features of the study population are reported in Table 1. According to definition, patients showed considerable heterogeneity ($I^2 > 75\%$) for ECOG – PS 0 and 1, for haemoglobin values, neutrophil-lymphocyte ratio (NLR) and CEA and peri-hilar cholangiocarcinoma; substantial heterogeneity (I^2: 51–75%) was observed for the other biliary malignancies, ECOG PS 2, total bilirubin, CA19-9, the treatment with gemcitabine and platinum and for chemotherapy duration. The other characteristics showed medium heterogeneity except for female and the presence of bone metastases which had null values.

In the unadjusted cohort the median survival was 8.6 months (95%C.I.: 7.8–9.3) with a 9-month survival rate of 48.3% (95%C.I.: 45.0–51.5). The pooled weighted 9-month mortality was 52.1% (95%C.I.: 45.4–58.7) showing substantial heterogeneity across hospitals (I^2: 70.3%).

Determinants of mortality within 9 months

Results from the multilevel mixed effect logistic regression are reorted in Table 2. Male had 1.86 higher odds for mortality. Being treated for gallblad- der cacer increased the odds by 1.81, in respect to all th other biliary malignancies. Additionally, higher the ECOG – PShigher the odds, being 2.39 for PS of 1 and 6.31for PS 2. An increase on 1 logarithm of NLR, of EA and of CA19-9 increased the odds for 9-month mortality f 3.33, 1.32 and 1.31, respectively. Finally, higher thehaemoglobin lowers the odds and, conversely, higher the ilirubin higher the odds for

Table 2. Determinants of mortality within 9 months of the 915 patients treated for biliary malignancies by multilevel mixed effects logistic regression.

	Simple regression		Multivariable	
Characteristic	HR (95%C.I.)	*P*	HR (95%C.I.)	*P*
Age (years)	1.02 (1.01–1.04)	0.002	1.01 (0.99–1.02)	0.265
Male	1.46 (1.12–1.90)	0.005	1.86 (1.37–2.53)	0.001
Malignancy				
Intra-hepatic	Ref.	–	Ref.	–
Peri-hilar (2)	0.98 (0.59–1.61)	0.939	Ref.	–
Distal (3)	1.07 (0.71–1.61)	0.751	Ref.	–
Gallbladder (4)	1.60 (1.15–2.22)	0.005	1.81 (1.27–2.58)	0.001
ECOG – PS				
0	Ref.	–	Ref.	–
1	2.96 (2.15–4.06)	0.001	2.39 (1.72–3.33)	0.001
2	11.1 (6.15–20.3)	0.001	6.31 (3.38–11.8)	0.001
Haemoglobin (g/dL)	0.78 (0.72–0.84)	0.001	0.83 (0.75–0.90)	0.001
Total bilirubin (mg/dL)	1.46 (1.22–1.73)	0.001	1.18 (1.01–1.39)	0.042
NLR (log10, ratio)	5.24 (3.20–8.57)	0.001	3.33 (1.96–5.66)	0.001
CEA (log10, mg/L)	1.67 (1.37–2.03)	0.001	1.32 (1.06–1.64)	0.012
CA19-9 (log10, U/mL)	1.48 (1.30–1.68)	0.001	1.31 (1.13–1.51)	0.001
Metastatic disease				
Peritoneal	1.36 (0.92–2.00)	0.119	–	–
Lung	1.05 (0.69–1.60)	0.804	–	–
Bone	1.82 (0.96–3.43)	0.067	–	–
Gemcitabine + platinum	0.57 (0.43–0.74)	0.001	0.75 (0.55–1.02)	0.170

The constant for the multivariable model was 0.85 (95%C.I.: 0.24–2.99).
The intraclass correlation coefficient was 2.6% (95%C.I.: 0.5–11.9) and this was the within-hospital residual variation not explained by the model.

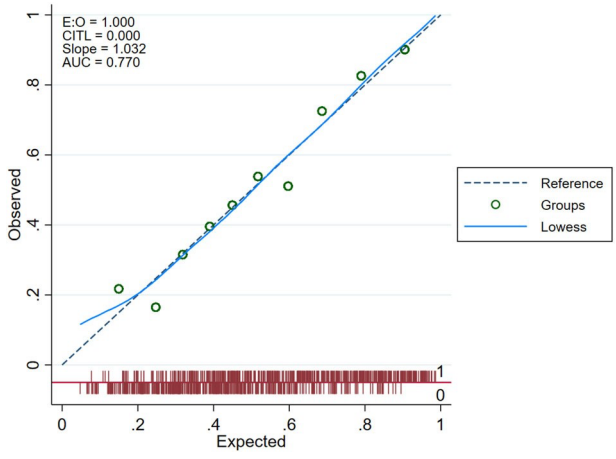

Figure 1. Calibration plot of the expected mortality within 9 months versus the observed rate. The model showed good calibration supporting the reliability of the subsequent risk-adjusted comparison between hospitals.

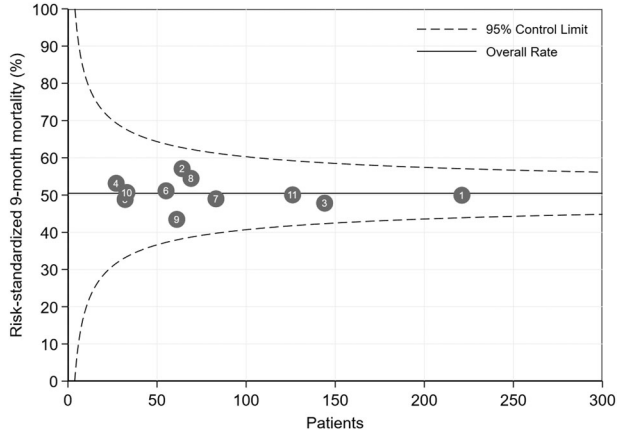

Figure 2. Risk-standardized 9-month mortality over 11 hospitals for all biliary malignancies. As noticeable, when adjusted for covariates all centres had mortality within respective confidence bands.

mortality within 9 months. Of note, the treatment with gemcitabine plus platinum was not independently related to mortality at multivariable model. The model estimated that the residual variance observed in 9-month mortality was attributable for the 2.6% to the treating hospital.

Risk-adjustment across hospitals

Expected mortalities within each centre were estimated through the multilevel mixed effect model. Figure 1 showed the calibration of the model which had a slope of 1.03 and a c-statistic of 0.770, providing good reliability of predicted estimates, suitable for risk-adjustment.

As detailed in Figure 2, the average risk-standardized mortality within 9 months was 50.1%. As noticeable, all hospital's risk-standardized mortality falls within 95%C.I., supporting that all participating centres can provide similar outcomes when adjusted for patient case-mix. This was confirmed when stratified for the specific malignancy considered (Supplementary Figures).

Discussion

In the present studmortality after risk-adjustment across hospitals highlighted no differences in term of

OS; despite a significant heterogeneity in term of hospital volume and patients' characteristic. In fact, our analysis included both tertiary institutions with high volume and high expertise, and small hospital with low volume of BTC patients. Many studies have demonstrated the importance of the institution's volume of treated patients in improving surgical outcomes in several cancer settings [9–15]. In our knowledge, this is the first study which investigates the role of the single institution and of its volume of treatments on survival outcomes of a sample of patients with advanced BTC treated with first line chemotherapy. Platin-based chemotherapy has been approved as standard first line treatment for advanced BTC in the last 10 years [2]. Moreover, both gemcitabine and cisplatin are established chemotherapy drugs, with a well-known spectrum of adverse events which physicians have managed along more than thirty years in different oncologic settings. The no impact of the institution and its volume of treatments on survival outcomes in our analysis can be partially related to the physicians' confidence in using drugs. In other words, the oncologists have learned how to manage the chemotherapy in high volume centres as well as in small hospitals, and no significant differences between centres have been revealed in terms of survival outcomes. If considering other settings, mainly those which require more recent treatments, the scenario could be different. For example, previous studies investigated the role of the physician's expertise in the survival outcomes of patients treated with multikinase inhibitors, which were introduced in clinical practice in the last 10 years. Casadei-Gardini and collaborators reported an improved PFS and OS in Sorafenib-receiving HCC patients managed by a dedicated physician compared to those who were not (HR 0.44, 95% C.I. 0.26–0.75, $P = 0.003$) [16]. The different outcomes could be explained by the multidisciplinary work and by a better management of the adverse events of multikinase inhibitors by the physician, thus leading to a better compliance to therapy by patients.

An important aspect that has to be considered is that patients included in our sample were treated before the advent of the new molecular target therapies in this setting, and for this reason the major part of the patients received standard chemotherapy. It will be interesting to investigate in future the impact of team's expertise in a cohort of BTC patients which includes also carrier of biological targets and treated with target therapies. In fact, in this era of precision medicine, this aspect can change over time. Recent progress in comprehensive genomic profiling for advanced BTC revealed recurrent driver genic alterations including FGFR2 fusion and IDH1 mutations, both targetable by new biological compounds which are currently under investigation in selected populations [17–19]. Moreover, the whole-exome and targeted sequencing of BTC highlighted mutations in novel chromatin remodelling-associated genes, including BAP1, ARID1A and PBRM1, which constitute promising targets for future researches [20]. The better understanding of comprehensive genomic profiling in BTC has led to the hope in personalized treatment for BTC patients. For this reason, we could suspect that the physician's confidence in using the new technologies to translate in clinical practice the new updated insights and to give to patients the possibility to be accrued in clinical trials could constitute an important factor influencing the survival outcomes. As clearly reported by the American Cancer Society Cancer Action Network, clinical trials are mandatory in translating basic research findings into the clinic with the aim to improve survival outcomes and quality of life of cancer patients [21]. Nevertheless, a huge variability between institutions exists from this point of view, thus affecting the outcomes.

A significant heterogeneity in term of patient's characteristics between hospital were found in this analysis. The relationship between hospital operative volumes and survival outcomes in several cancer disease, and the consequently trend to the surgical centralization in the so-called 'Centres of Excellence' is already well-established [22]. Starting from the complexity of the BTC's surgical management, we hypothesized that the heterogeneity revealed in our analysis might be indirectly related to the different surgical expertise of each institution, and to the trend toward a centralization of patients with different subtype of BTC in specific centre, thus inducing a kind of selection bias.

Secondly, with the aim to investigate the possible prognostic factors after reducing the confounding elements, we performed a risk-adjusted analysis, and revealed that the male gender, the gallbladder cancer, a higher ECOG PS, high level of NLR, CEA, Ca 19.9 and serum bilirubin as well as low level of serum haemoglobin are all related to a higher risk of death. Our results are consistent with previous data. In particular, several studies highlighted the prognostic role of gender, ECOG PS and others bio-humoral parameters [23–26]. Unexpectedly, the chemotherapy with cisplatin and chemotherapy resulted to impact on survival in advanced BTC patients in univariate analysis, whereas no prognostic significance was showed in

multivariate. The ABC-02 trial led to the approval of the regimen gemcitabine plus cisplatin as first standard therapy in the advanced BTC setting, since the double regimen showed a statistically significant improvement compared gemcitabine monotherapy. For sure, we could not compare the results from a prospective registry trial with our results, which derived from a retrospective analysis. Moreover, we evaluated a large sample of patients treated with different regimens, which included gemcitabine plus cisplatin and gemcitabine in monotherapy, but not only, since we considered multiple chemotherapy regimens, thus confounding our results. On the other hand, a possible underestimation of the impact of the first line standard of care could be related to the statistical method. In the multivariate analysis we included several factors which could be directly or indirectly related to the chemotherapy and to the choice of the most adequate regimen. In particular, several clinical factors are directly related to the decision to treat or not a patient with systemic therapy (for example: ECOG PS); other factors, including bio-humoral factors, are included in the integrative evaluation of patients and in the decision of a regimen instead of another regimen. For this reason, the inclusion of these factors in the multivariate analysis could has acted as confounder in terms of survival outcomes.

The present study has some limitations, basically due to the retrospective nature of the analysis, which could not completely exclude selection bias. In order to reduce bias, we performed a first step risk-adjusted analysis on a number of institutions: by expanding the analysis to a higher number of oncological centres it might be possible to obtain more powerful data. Nevertheless, the survival results of our analysis are homogeneous thus suggesting the adoption of the best personalized treatments for patients in the institutions involved.

In conclusion we here showed that in multicentric national cohort, a heterogenicity between hospital in term of patients treated were found but this didn't affect the outcome in term of overall survival. More insights are needed in order to identify the role of the physician's expertise, mostly in vision of a growing interest in new diagnostic technologies and new therapeutic strategies.

Author contributions

Conception and design: A. Casadei-Gardini, M. Rimini. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: A. Casadei-Gardini, M. Rimini. Writing, review, and/or revision of the manuscript: A. Casadei-Gardini, M. Rimini. All authors approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

Data are available on request from the authors.

Informed consent statement

Written informed consent for treatment was obtained for all patients.

Institutional review board statement

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

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