Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-020-00526-5

ORIGINAL RESEARCH

Incidence and Prognosis of Biliary Tract and Gallbladder Cancers in a Belgian Academic Hospital

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Accepted: 20 September 2020

Abstract

Background Biliary tract and gallbladder cancers are rare tumors with a poor prognosis (except the ampulla type). The evolution of hepatobiliary cancer incidence varies widely around the world. According to the Belgian Cancer Registry, the number of hepatobiliary cancers has increased every year since 2004.

Materials and Methods This retrospective study included patients diagnosed with cholangiocarcinoma, ampulla cancer, or gallbladder cancer at the university hospital, CHU UCL, Godinne site, in Namur, Belgium, between 1997 and 2017. The evolution of cancer incidence was evaluated with the Mann-Kendall method, by analyzing 7 consecutive 3-year periods. We calculated survival with the Kaplan-Meier method, and we determined prognostic factors with the log-rank test and Cox models.

Results Between 1997 and 2017, we included 128 patients that were newly diagnosed in our center. According to the Mann-Kendall test, the evolution of the incidence of these cancers in our hospital increased significantly over the study period (Sen's slope = 7; $p = 0.003$). The 1-year overall survival was 53.0 ± 4.7%. Poor prognostic factors included age, cancer stage, local cancer extension, and metastatic disease. The independent prognostic factors of survival were age ($p = 0.002$), ampulla cancer ($p < 0.001$), and metastatic disease ($p < 0.001$).

Conclusions We found that the incidence of biliary tract and gallbladder cancers increased over a period of 20 years in our center. Further investigations are needed to determine the reasons for this increase. Although new therapies are emerging, the prognosis remains poor for these cancers. Determining risk factors might promote the development of preventive approaches.

Keywords Cholangiocarcinoma · Epidemiology · Belgium · Risk factor · Survival

Abbreviations

CHU	Centre Hospitalier Universitaire
UCL	Université Catholique de Louvain
HR	Hazard ratio
CI	Confidence interval
BMI	Body mass index

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Introduction

Biliary tract and gallbladder cancers are rare tumors, but the evolution of their incidences varies widely around the world [1]. These cancers include ampullary cancer, vesicular carcinomas, and cholangiocarcinomas, which are typically categorized anatomically as intrahepatic, hilar, and extrahepatic cancers.

Globally, in areas with a high risk of liver cancer, particularly Eastern and Southeastern Asian countries, the incidence of liver cancers (hepatocarcinoma and intrahepatic cholangiocarcinoma) has decreased between 1978 and 2007. However, in low-risk countries, this incidence has increased over time [1]. In Europe, between 2000 and 2007, the incidence of

Published online: 28 September 2020

biliary tract and gallbladder cancers was relatively stable [2]. But, the specific incidences of different anatomical and histological subtypes have evolved differently in some countries. For example, the rates of intrahepatic cholangiocarcinoma in Thailand, France, and Italy have increased, even though the rate of hepatocarcinoma decreased [1]. In the USA, the incidence of intrahepatic cholangiocarcinomas has increased, and the rate of extrahepatic appeared to remain stable [3]. Finally, in Belgium, according to the Belgian Cancer Registry, the number of hepatobiliary cancers has increased every year since 2004 [4].

The variability in the incidence of hepatobiliary cancers around the world and over time suggests that environmental risk factors, and probably polymorphism genetics, are involved [5]. The main identified risk factor for biliary tract and gallbladder cancers was an infection by liver flukes, like *Clonorchis sinensis* or *Opisthorchis viverrini*, which are basically found in Eastern and Southeastern Asia [6, 7]. These parasites cause neoplasia by inducing a chronic inflammation of the bile ducts. Then, through the proliferation of reactive cells, oncogenic mutations can occur [8]. In Western countries, the main risk factors for biliary tract and gallbladder cancers are pathologies that activate the same molecular pathways that induce chronic inflammation or cholestasis [8]. Consequently, these cancers are frequently associated with primary sclerosing cholangitis, choledochal lithiasis, inflammatory bowel disease, tobacco use, excessive alcohol consumption, chronic liver disease, diabetes, and hepatitis B and C [5, 8, 9]. Accordingly, chronic inflammation and obstruction of biliary flow are the two main risk factors recognized in western countries [8].

The purpose of this study was to assess the evolution of the incidences of biliary tract and gallbladder cancers in an academic hospital in Belgium over the last 20 years. These data might reflect the evolution of the incidence of hepatobiliary disease in Belgium. Furthermore, we analyzed our patient population to investigate environmental factors that might explain the observed variations in incidence. Finally, we analyzed overall survival and patient characteristics to identify potential prognostic factors.

Materials and Methods

This retrospective study included all patients newly diagnosed with cholangiocarcinoma, ampulla cancer, or gallbladder cancer at the university hospital, CHU UCL, Godinne site, in Namur, Belgium, from 1997 to 2017. We identified a cohort of 128 patients, based on anatomopathology data, systematic minimum clinical summaries, and the cases discussed in multidisciplinary oncology discussions.

We then collected the following data from patient computer files: disease stage, date of diagnosis, date of death, sex, age at diagnosis, presence of metastasis at diagnosis, treatment received, date of first recurrence, excessive alcohol and tobacco consumption, presence of inflammatory bowel disease and/or cirrhosis, and patient weight and height at diagnosis. Next, we evaluated the evolution of disease incidence with the Mann-Kendall test, over seven consecutive 3-year periods (1997–1999, 2000–2002, 2003–2005, 2006–2008, 2009–2011; 2012–2014, 2015–2017) and calculated Sen's slope. We applied the Kaplan Meier method to estimate patient survival, and we constructed survival curves. We determined prognostic factors with the log-rank test for categorical variables and with a Cox model for numerical variables. We also used a Cox proportional hazards model for a multivariable analysis of survival.

We performed all statistical analyses with MedCalc 19.1 software (MedCalc Software, Ostend, Belgium).

This retrospective study was approved by the Ethics Committee of the CHU UCL Godinne site, Namur.

Results

Between 1997 and 2017, 128 patients were diagnosed with hepatobiliary cancers in our center. Among these patients, 20% had ampulla cancer, 77% had cholangiocarcinoma, (including 38% intrahepatic cancer, 16% hilar cancer, and 23% extrahepatic cancer), and 3% had gallbladder cancer (Table 1).

According to the Mann-Kendall test, the incidences of these cancers increased significantly in our center over the study period. We observed a Sen's slope of 7, which corresponded to 7 additional new cases in each successive 3-year period ($p = 0.003$; Fig. 1). We also evaluated the incidence by tumor location. This analysis indicated that the incidence of cholangiocarcinomas increased, particularly the intrahepatic subtype, and the incidences of ampulla and gallbladder cancers remained stable.

Our population consisted of 67 males and 61 females, and the average age was 68.6 ± 11.9 years. Of the 128 patients, 47 were smokers, 15 consumed more than 3 units of alcohol per day, 9 had a diagnosis or a history of cirrhosis, and 24 had diabetes. Treatments included surgery ($n = 37$), chemotherapy ($n = 64$), and supportive care only ($n = 28$). The average body mass index (BMI) was 26.4 ± 5.6 kg/m^2.

Table 2 shows the results of univariate and multivariate survival analysis. All variables discussed are entered into the multivariate Cox proportional hazards model. The factors which significantly influence survival were age with a hazard ratio (HR) of 1.034 with 95% confidence interval (CI) 1.012 to 1.056 ($p = 0.002$), the ampulla anatomic location which had a better survival than the other locations (HR = 5.084; IC = 1.957–13.214; $p < 0.001$), and the presence of metastasis which had a worse prognosis (HR = 3.321; IC = 1.877–5.875; $p < 0.001$). Replacing the presence of metastasis by

Table 1 Characteristics of 128 patients with biliary tract and gallbladder cancers

Characteristics	Number of patients[a]					
	Global	Adenocarcinoma location				
		Intrahepatic	Hilar	Extrahepatic	Ampulla	Gallbladder cancer
Number of patients, *n* (%)	128 (100)	48 (38)	20 (16)	30 (23)	26 (20)	4 (3)
Male, *n* (%)	67 (52)	20 (42)	12 (60)	18 (60)	16 (62)	1 (25)
Mean age at diagnosis, years (range)	69 (42–97)	66 (42–91)	71 (43–94)	72 (53–97)	68 (45–84)	66 (53–85)
TNM staging, *n* (%)						
- T1	8 (11)	2 (7)	0 (0)	2 (14)	4 (22)	0 (0)
- T2	24 (34)	12 (43)	2 (29)	2 (14)	6 (33)	0 (0)
- T3	30 (42)	9 (32)	4 (57)	9 (64)	6 (33)	2 (50)
- T4	9 (13)	5 (28)	1 (14)	1 (7)	2 (11)	2 (50)
- N0	26 (39)	7 (28)	3 (43)	7 (54)	8 (44)	1 (25)
- N1	39 (58)	18 (72)	4 (57)	5 (38)	9 (50)	3 (75)
- N2	2 (3)	0 (0)	0 (0)	1 (8)	1 (6)	0 (0)
- M0	48 (49)	13 (30)	2 (18)	13 (72)	18 (86)	2 (50)
- M1	49 (51)	30 (70)	9 (82)	5 (28)	3 (14)	2 (50)
Stage at diagnosis, *n* (%)						
- I	10 (11)	1 (2)	0 (0)	2 (12)	7 (35)	0 (0)
- II	14 (15)	2 (5)	0 (0)	7 (41)	5 (25)	0 (0)
- III	20 (21)	8 (19)	2 (18)	3 (18)	5 (25)	2 (50)
- IV	50 (53)	31 (74)	9 (82)	5 (29)	3 (15)	2 (50)
Treatment received[b], *n* (%)						
- Surgery	37 (34)	6 (13)	2 (12)	9 (41)	17 (81)	3 (75)
- Chemotherapy	64 (59)	34 (74)	7 (41)	13 (59)	7 (33)	3 (75)
- Best supportive care at diagnosis	28 (26)	10 (22)	9 (53)	6 (27)	3 (14)	0 (0)
Smokers, *n* (%)	47 (45)	23 (50)	7 (41)	4 (20)	7 (39)	1 (25)
Excessive alcohol consumption (more than 3 units of alcohol per day), *n* (%)	15 (14)	8 (18)	3 (18)	1 (5)	1 (6)	0 (0)
Inflammatory bowel diseases, *n* (%)	3 (3)	2 (4)	1 (5)	0 (0)	0 (0)	0 (0)
Cirrhosis[c], *n* (%)	9 (8)	7 (15)	2 (10)	0 (0)	0 (0)	0 (0)
Etiology:						
- Alcoholic	6 (5)	6 (13)	0 (0)	0 (0)	0 (0)	0 (0)
- HBV	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
- Unknown	2 (2)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)
Mean body mass index, kg/m^2 (SD)	26.4 (5.6)	26.4 (4.9)	25.9 (6.0)	27.1 (6.6)	25.0 (3.6)	31 (12.0)
Diabetes, *n* (%)	24 (20)	8 (17)	4 (20)	6 (24)	4 (18)	2 (50)

[a] Patients with missing variables were not included in percentage calculations

[b] Some patients received both surgical and chemotherapy treatments

[c] In our retrospective study, liver cirrhosis was established as soon as the diagnosis was mentioned in the medical file

the stage of the disease leads to an equivalent model, both factors being interchangeable.

The prognosis for 1-year overall survival was higher for ampulla cancer (80.9% ± 8.6%) compared with intrahepatic cancer (40.5 ± 7.4%), hilar cancer (46.3 ± 12.4%), and extrahepatic cholangiocarcinoma (55.6 ± 9.6%; $p < 0.001$ for all; Fig. 2).

Finally, intrahepatic cholangiocarcinoma had a lower progression-free survival than the extrahepatic cholangiocarcinoma with a HR of 2.145 with 95% CI 1.332 to 3.456 ($p = 0.002$; Fig. 3). However survival did not differ significantly.

Discussion

This study showed that the incidences of biliary tract and gallbladder cancers increased in a Belgian center over the last

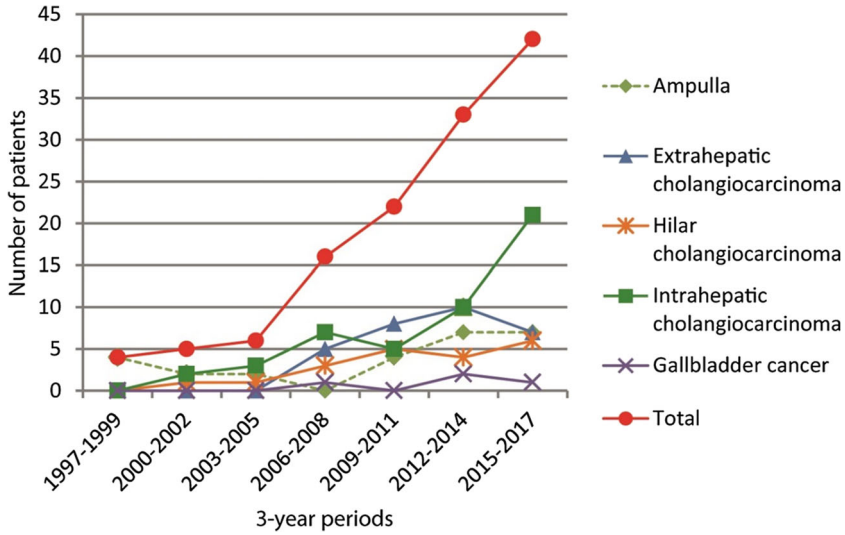

Fig. 1 Evolution of the incidence of biliary tract cancers in CHU Namur, Godinne site. Cancer subtypes are grouped according to the anatomical location. Incidences are calculated for 3-year periods

20 years, as expected. Indeed, the Belgian cancer registry reported that the total number of liver, gallbladder, and biliary tract cancers rose in Belgium, from 705 in 2004 to 1404 in 2017 [4]. Therefore, our sample appeared be representative of

Table 2 Univariate and multivariate analysis of survival according to the Cox model

			Univariate analysis				Multivariate analysis (Cox)			
Factor	Class	Median survival (years)	Hazard rate	95% inf CI for HR	95% sup CI for HR	*p*	Hazard rate	95% inf CI for HR	95% sup CI for HR	*p*
Gender	M	1.339	1.000							
	F	0.961	1.446	0.955	2.189	0.073				
Age	Per year		1.019	1.001	1.038	0.040	1.034	1.012	1.056	0.002
T	1	3.461	1.000							
	2	1.432	1.932	0.894	4.179					
	3	1.295	2.436	1.131	5.249					
	4	0.827	2.984	1.004	8.874	0.217				
N	0	2.593	1.000							
	1	1.092	1.816	1.030	3.200					
	2	1.355	1.308	0.187	9.118	0.127				
M	No	2.231	1.000							
	Yes	0.786	2.878	1.752	4.726	< 0.001	3.321	1.877	5.875	< 0.001
Stage	1	10.593	1.000							
	2	1.574	2.514	1.221	5.178					
	3	2.231	2.402	1.233	4.680					
	4	0.701	6.286	3.328	11.872	< 0.001				
Localization[a]	Ampulloma	10.593	1.000							
	Hilar	0.720	4.393	2.086	9.251					
	Intrahepatic	0.794	3.803	2.285	6330					
	Extrahepatic	1.295	2.634	1.535	4.520	< 0.001				
	Ampulloma	10.593	1.000							
	Others	0.931	3.445	2.235	5.311	< 0.001	5.084	1.957	13,214	< 0.001

Hazard ratios (= HR) calculated for overall survival with a 95% confidence interval (= CI)

[a] We analyzed the hazard rate between each location. Gallbladder adenocarcinoma was excluded from this analysis because it only included 4 patients. The ampulloma was then compared with all the others

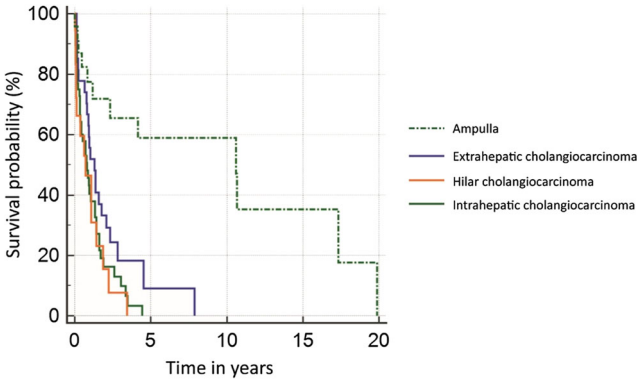

Fig. 2 Kaplan-Meier curves show overall survival for patients with biliary tract cancers. Cancer subtypes are grouped according to anatomical location

the general population of Belgium. We found that the largest increase was observed in the incidence of intrahepatic cholangiocarcinomas, and a slightly lower increase was observed in the incidence of extrahepatic cholangiocarcinomas. In contrast, the incidences of ampulla and gallbladder cancers remained stable. These observations emerged also by the Belgian cancer registry with 61 cases of intrahepatic cholangiocarcinomas diagnosed in 2004 to 194 in 2017 (Fig. 4) [4]. Contrariwise, the incidence of extrahepatic cholangiocarcinomas in Belgium is stable [4]. The different evolutions we observed in cancer incidences for the different anatomical subtypes were similar to those observed in the USA and in Germany [3–10].

Further investigations are needed to determine the reasons for the observed increases in biliary tract and gallbladder cancer incidences. Our study population included predominantly individuals with smoking habits (45%) and some displayed excessive alcohol consumption (14%). These characteristics occurred more frequently than they occurred in the Belgian Health Interview Survey, which estimated prevalences of 23.0% and 6.4%, respectively, in 2013 [11]. In addition, alcohol, tobacco, and cirrhosis were characteristics observed in our study in bigger proportion in intrahepatic cholangiocarcinomas than in extrahepatic cholangiocarcinomas. The association with alcohol and cirrhosis was stronger with intrahepatic cholangiocarcinomas than with extrahepatic cholangiocarcinomas [9]. However, their prevalences in Belgium have been decreasing, according to Belgian Health Interview Survey, and could not explain the increased incidence of intrahepatic cholangiocarcinoma in Belgium. Moreover, our patients tended to be overweight (BMI >25 kg/m^2), and 20% had diabetes at diagnosis. These are also known risk factors of biliary tract and gallbladder cancers. Among the general population of Belgian patients with diabetes mellitus, the prevalence of biliary tract and gallbladder cancers is currently about 4.39%, but it has been increasing since 1997, according to the Belgian Health Interview Survey [11, 12]. Thus, these conditions could be considered environmental factors that might explain the observed increases in the incidences of biliary tract and gallbladder cancers in Belgium [11].

The only curative treatment for hepatobiliary cancers is radical surgery, and only when the resection margins are healthy. Thus, when surgery is performed in the early, resectable stages, the 5-year survival rates range from 20 to 44%. Unfortunately, biliary tract and gallbladder cancers are frequently diagnosed at advanced stages, because they are often sustainably asymptomatic. Therefore, due to the preponderance of unresectable advanced disease, the 5-year survival rate is only about 5% (except for ampulla cancer) [5, 13]. In addition to the local extent of disease, localization, and age, other prognostic factors not studied or demonstrated in our study have been described in patients with unresectable biliary tract cancers. Prognostic factors associated with poor progression-free survival and poor overall survival include an Eastern Cooperative Oncology Group performance status ≥ 2, high neutrophil levels, high bilirubin levels, low hemoglobin levels, low white blood cell levels, male sex, and metastatic disease [14].

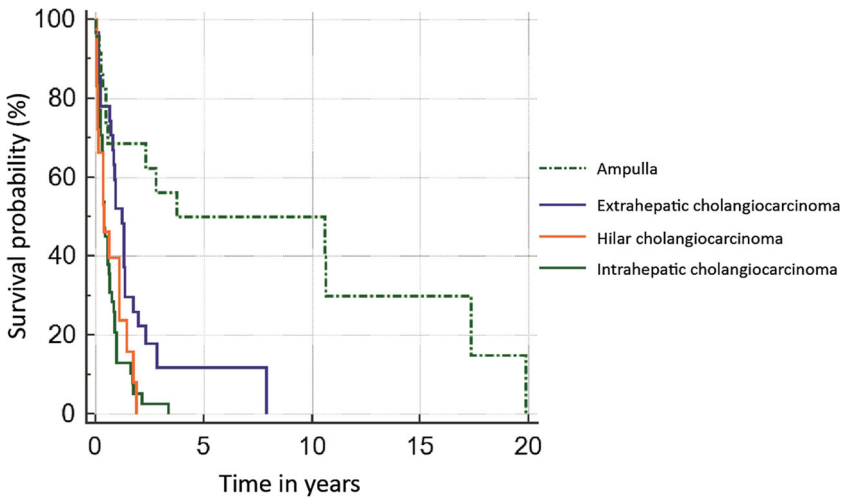

Fig. 3 Kaplan-Meier curves show progression-free survival for patients with biliary tract cancers. Cancer subtypes are grouped according to anatomical location

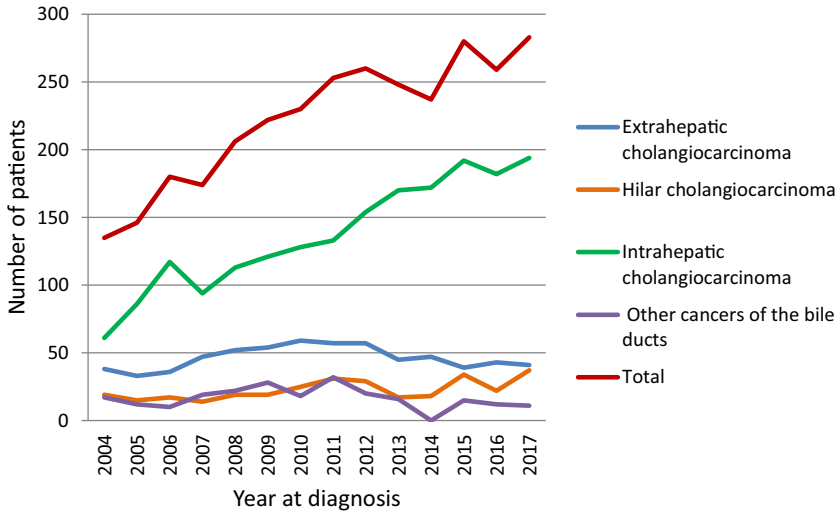

Fig. 4 Evolution of the incidence of biliary tract cancers in Belgium. Cancer subtypes are grouped according to the anatomical location. This figure produced with data from the Belgian Cancer Registry [3]

The 5-year overall survival rate was 12.3 ± 3.8% in our population. This poor prognosis was comparable with that observed in the European population (5-year survival = 6% for intrahepatic cholangiocarcinomas, 14.5% for gallbladder adenocarcinomas, and 19.2% for extrahepatic adenocarcinomas) [5, 13]. These poor prognoses are linked to the often late discovery of these cancers. In our study, about 1 out of 2 patients displayed metastasis at diagnosis. To improve survival, we need an effective screening tool for earlier detection.

Between 1997 and 2017, the computerization of our university hospital and diagnostic accuracy improved. The biliary tract and gallbladder cancers have therefore been better and better referenced, which alone can increase our local incidence and cause bias. Improvements in histopathological techniques have increased the accuracy of diagnosing cholangiocarcinoma, particularly the intrahepatic subtype. Concomitantly, fewer patients have been diagnosed with unknown primary cancers in an US study [3]. Intrahepatic cholangiocarcinomas in Belgium could also have been misclassified in the past [3, 9].

Due to some potential study limitations, care must be taken in generalizing the results of this retrospective descriptive study. Indeed, we had an important selection bias, due to the population from only one center, which represented an academic community. Therefore, our study might not have represented the entire Belgian population; however, the evolution of incidences in all of Belgium appeared to be similar to those revealed in our study population.

Conclusions

We found an increase, over time, in the incidence of biliary tract cancers particularly intrahepatic cholangiocarcinomas and more slightly the extrahepatic, in our Belgian academic hospital. Ampulla and gallbladder cancers remained stable. This increase was consistent with a similar increase in the incidence of this disease in the general Belgian population [4]. Despite therapeutic progress, the prognosis of these cancers remains poor. Identifying risk factors for these cancers could promote the development of preventive approaches. With the limitations of this retrospective study, we identified overweight status, diabetes, tobacco use, and excessive alcohol consumption as environmental factors that seemed to be associated the development of these cancers. Currently, action is needed to target these factors, particularly diabetes and obesity, which are becoming increasingly prevalent in Belgium [11].

Acknowledgments The authors would like to thank the participating patients and their families.

Availability of Data and Material Not applicable.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

Ethical Approval This retrospective study was approved by the Ethics Committee of the CHU UCL Godinne site, Namur.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

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