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Time to use the right classification to predict the severity of checkpoint inhibitor-induced liver injury, as assessed for causality using the updated RUCAM

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Summary

Background and Aims: While immune checkpoint inhibitors (ICIs) are revolutionising cancer therapy, checkpoint inhibitor-induced liver injury is a significant immune-related side effect of this immunotherapy. This study focuses on the severity classifications and characteristics of patients with checkpoint inhibitor-induced hepatitis.

Methods: A retrospective analysis of patients with severe Checkpoint Inhibitor-induced hepatitis grade 3 and 4 according to the recommended Common Terminology Criteria for Adverse Events (CTCAE) classification was conducted. Data on clinico-biological characteristics, treatment and outcomes were collected from 3 university hospitals, and causality was assessed by using the updated Roussel Uclaf Causality Assessment Method. The severity of hepatitis was assessed using the Model for

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End-stage Liver Disease score, the Drug-Induced Liver Injury Network, and the Drug-Induced Liver Injury International Expert Working Group classifications.

Results: We retrospectively included 100 patients presenting various hepatitis patterns with a median time to onset of 20 days after checkpoint inhibitors. Severity grading varied significantly among the classifications used. A lower incidence of severe cases was observed when using the Drug-Induced Liver Injury classifications instead of the recommended CCTCAE classification, and this was correlated with outcomes.

Conclusions: This retrospective study challenges the efficacy of the CTCAE classification in defining the severity of Checkpoint Inhibitor-induced hepatitis and suggests that the traditional hepatology-focused scores may be more relevant. The CTCAE classification is inconsistent and gives equal weight to jaundice and elevated transaminases, which leads to steroid overtreatment and limits the rechallenge of ICIs.

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) are blocking monoclonal antibodies targeting immune checkpoint, whose activation inhibits T-mediated antitumor response.[1] ICIs have revolutionised cancer therapy and have been approved by international drug safety agencies since the early 2010s.[2] The most prescribed ICIs in clinical practice target PD-1 (programmed cell death-1), its ligand PDL-1 (programmed cell death ligand-1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein-4).[3] To date, ICIs have increasing indications, and are indicated as first-line treatments for many advanced solid cancers as adjuvant, neoadjuvant and maintenance therapy.[2,4] However, the outstanding efficiency of ICIs is associated with the onset of multisystemic immune-related adverse events (irAEs), with varying degrees of severity, due to a loss of self-tolerance when antitumor T-mediated immunity is restored.[5] Checkpoint inhibitor-induced liver injury (CHILI) is one of the main side effects of ICI and may occur in up to 30% of patients treated with ICIs.[6] Recently, a retrospective study showed that the real risk of CHILI is greater than described in the literature, with an overall incidence rate of 11.5 per 1000 person-months.[7] A meta-analysis published in 2018 showed that CHILI accounted for 17% of fatal adverse events, among patients treated with anti-PD(L)1.[8] Oncological international guidelines use The Common Terminology Criteria for Adverse Events (CTCAE) v5 to grade the severity of irAEs from grade 1 (mild) to 5 (fatal toxicity),[9–11] and CHILI management is proposed according to these grades. Although the CTCAE classification does not consider liver function, the EASL and AASLD guidelines recommend liver function assessment to evaluate the severity of drug-induced liver injury (DILI).[12,13] Validated grading classifications for DILI are US Drug-Induced Liver Injury Network (DILI-N), which ranges from grade 1 (mild) to 5 (fatal toxicity), and International DILI Expert Working Group (DILI-IEWG), which ranges from grade 1 (mild) to 4 (fatal toxicity).[14,15] In addition, the growing use of ICI has led to the emergence of CHILI with acute liver failure (ALF).[16–19] According to the current guidelines, ALF is defined by markers of liver damage (elevated serum transaminases) associated with impaired liver function (jaundice and INR ≥1.5) and clinical encephalopathy.[20] Acute liver injury (ALI) is defined by impaired liver function without clinical encephalopathy.[20] Drug-induced liver injury (DILI), especially paracetamol-related liver injury, is the most frequent cause of ALI and ALF, and may require liver transplantation (LT).[20] Also, the Model for End-stage Liver Disease (MELD) score, which has been validated and used to predict the prognosis of cirrhotic patients, appears to be suitable in predicting poor outcomes in DILI patients.[21,22] Identifying CHILI with liver dysfunction is a growing challenge and it would enable us to recognise patients at risk of poor outcomes. The aim of this study is to compare the CTCAE, MELD score, DILI-N and DILI-IEWG classifications to predict the occurrence of ALI in patients with CHILI.

2 | MATERIALS AND METHODS

2.1 | Patients and data collection

We conducted a multi-center retrospective study of consecutive CHILI patients discussed during "ToxImmun" multidisciplinary meetings between December 2018 and November 2023 at Montpellier University Hospital. The patient files were submitted from Montpellier University Hospital, Montpellier Cancer Institute and Nimes University Hospital. Inclusion criteria were (i) adult patients treated by ICI; (ii) patients with previous normal liver tests, defined as normal transaminases, ALP, GGT and bilirubin levels; (iii) CHILI presentation with abnormal liver tests, after ruling out other causes of hepatitis; and (iv) CHILI grade CTCAE 3 (severe) or 4 (life-threatening). Patients with underlying liver disease and normal baseline liver tests were included. Patients on anticoagulants with uninterpretable international normalised ratio (INR) value were excluded. Clinical and biological CHILI-related data were collected at diagnosis; at weeks 1, 2, and 4; and then monthly until recovery from

hepatitis. Data regarding cancer, treatment of CHILI, and ICI rechallenge were also collected.

2.2 | Definitions and outcomes

All patients were referred to the hepatologist and underwent an extensive evaluation to exclude other potential causes of liver enzyme abnormalities, such as viral hepatitis, autoimmune disease, cancer progression, vascular complications, or other treatments causing DILI. Liver imaging (ultrasound, computed tomography, or magnetic resonance imaging) was systematically performed. CHILI was diagnosed at onset using the updated Roussel Uclaf Causality Assessment Method (RUCAM), which aims to assess DILI causality[23]; CHILI was defined as possible (RUCAM 3–5), probable (RUCAM 6–8), and highly probable (RUCAM ≥9). CHILI CTCAE G3 and G4 were included, and severity was graded at onset according to (i) MELD score, (ii) DILI-N classification (the US severity classification) and (iii) DILI-IEWG classification (the European severity classification, which is the RUCAM severity classification).[14,15] The DILI-N and DILI-IEWG scores have been measured according to the presence of jaundice, INR value ≥1.5, hospitalisation, liver or other organ failure, and death. Table S1 shows the thresholds used to define CTCAE, DILI-N and DILI-IEWG grades of hepatotoxicity. Hyperbilirubinemia was defined as total bilirubin ≥ N, and jaundice was defined as hyperbilirubinemia ≥42.5 μmol/L.[24] CHILI severity was classified as non-severe (grades 1–2) and severe (grades 3–4) for each severity classification (i.e. DILI-N, DILI-IEWG), and we compared G3 to G4 for CTCAE severity. Liver biopsy was performed based on the referring physician's discretion, and liver histology has been blinded-analysed by an expert pathologist. The hepatitis pattern was analysed by the serum ALT and ALP ratio (R value = (ALT/ULN)/(ALP/ULN), and classified as cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($2 < R < 5$)). ALT and ALP thresholds were indicated by each laboratory, as the blood tests were carried out both in the hospital and in external laboratories. The primary endpoint was the occurrence of liver dysfunction, defined as ALI, i.e. jaundice (hyperbilirubinemia ≥42.5 μmol/L) and INR ≥1.5. Secondary endpoints were hospitalisation, hepatic encephalopathy, use of a second-line immunosuppressant, plasmapheresis, 3-month mortality, and overall mortality.

2.3 | Statistical analysis

Descriptive statistics are presented as medians (ranges) and mean (SD) for quantitative variables and counts (percentages) for qualitative variables. The Wilcoxon rank sum test was applied to compare the distribution of continuous variables and chi-squared test (or Fisher's exact test when appropriate) was used to test the association of categorical variables. A $p < 0.05$ was considered statistically significant and all statistical tests were two-sided. Survival curves were calculated using the Kaplan–Meier method and compared with the log-rank test. We used Receiver-Operating Characteristic curves to assess the ability to predict ALI according to CTCAE, DILI-N and DILI-IEWG. The area under the curve and 95% confidence intervals were calculated. DeLong test was performed to make pairwise comparisons of the predictive variables CTCAE, DILI-N and DILI-IEWG according to ALI. Youden index was used to select an optimal threshold value or cutoff point, based on the receiver-operating

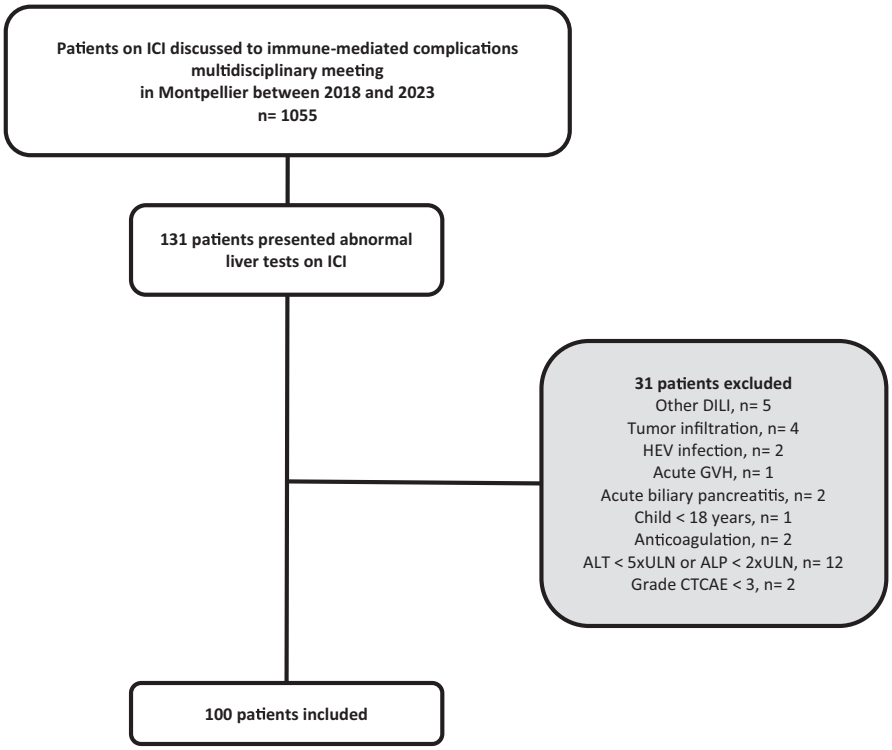

FIGURE 1 Flow chart.

TABLE 1 Characteristics of patients with immune checkpoint-induced liver injury (CHILI).

	N = 100
Age at diagnosis (years), median (range)	64.7 (23–88)
Sex, *n* (%)	
Female	42 (42)
Male	58 (58)
Medical history, *n* (%)	
Chronic alcohol consumption	8 (8)
Autoimmune disease	2 (2)
Anti-HBc IgG	6 (6)
Liver transplant	1 (1)
Pre-existing liver disease, *n* (%)	
Liver metastasis	7 (7)
Cirrhosis	4 (4)
Cancer, *n* (%)	
Lung	33 (33)
Melanoma	32 (32)
Renal and urothelial	20 (20)
Other cancers[a]	15 (15)
Cancer stade, *n* (%)	
Stade III	14 (14)
Stade IV	48 (48)
Not evaluable	38 (38)
Checkpoint inhibitor, *n* (%)	
Anti-PD1	64 (64)
Anti-PDL1	8 (8)
Anti-PD1 + anti-CTLA4	28 (28)
Concomitant oncologic treatment, *n* (%)	
Chemotherapy	15 (15)
Tyrosine kinase inhibitor	85 (85)
RUCAM, median (range)	8 (4–12)
RUCAM, *n* (%)	
Possible (3–5)	6 (6)
Probable (6–8)	50 (50)
Highly probable (≥9)	44 (44)
Laboratory liver tests, median (range)	
ALT (IU/L)	274 (22–3111)
AST (IU/L)	161 (23–4400)
GGT (IU/L)	327 (10–2216)
ALP (IU/L)	228 (38–2459)
Total bilirubin (μmol/L)	11 (3–300)
Hyperbilirubinemia (total bilirubin >ULN), *n* (%)	26 (26)
Jaundice (total bilirubin ≥2 ULN), *n* (%)	19 (19)
INR	1 (0.8–2.8)
Peak INR ≥1.5, *n* (%)	9 (9)
Liver biopsy, *n* (%)	37 (37)
Hospitalisation, *n* (%)	16 (16)
CTCAE severity score, *n* (%)	
Grade 3	73 (73)
Grade 4	27 (27)
MELD score, median (median)	7 (6–26)
DILI-N severity score, *n* (%)	
Grade 1	82 (82)
Grade 2	4 (4)
Grade 3	9 (9)
Grade 4	5 (5)
DILI-IEWG severity score, *n* (%)	
Grade 1	82 (82)
Grade 2	11 (11)
Grade 3	7 (7)

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DILI-IEWG, Drug-induced liver injury International Working Group; DILI-N, Drug-induced liver injury Network; GGT, Gamma-glutamyl transferase; INR, International normalised ratio; RUCAM, updated Roussel Uclaf Causality Assessment Method[23]; TBL, total bilirubin; ULN, upper limit of normal.

[a]Head and neck cancer, hepatocellular carcinoma, colorectal cancer, oesophageal cancer, breast cancer, intestinal T-cell lymphoma.

characteristic curve. Easymedstat software was used for statistical analysis (version 3.30.2; www.easymedstat.com). This study was conducted in accordance with both the Declarations of Helsinki and Istanbul. Institutional review board approval (IRB ID 202100908) and the written informed consent of each patient were obtained.

3 | RESULTS

3.1 | Patients' characteristics

A total of 100 patients with severe CHILI according to CTCAE (G3 and G4) were included in the study (Figure 1). Clinical characteristics of CHILI cases are indicated in Table 1. The median updated RUCAM score was 8 (probable) [6 "possible"; 50 "probable"; 44 "highly probable"], and the median age was 64.7 (23–88) years, with a sex ratio of 1.4 (58 males). ICIs were mostly used to treat lung carcinoma ($n = 33$), melanoma ($n = 32$), and renal cell carcinoma ($n = 20$). Most patients received PD-1 inhibitors, either alone ($n = 64$) or with a CTLA-4 inhibitor ($n = 28$), and concurrent chemotherapy or TKI (tyrosine kinase inhibitor) were respectively given in 15% and 13%. CHILI pattern was hepatocellular in 42%, cholestatic in 39%, and mixed in 19% of patients. Median delay from last ICI infusion until CHILI was 20 days (1–175). Twenty-six patients had bilirubinemia ≥ULN (26%), including 19 patients with jaundice (73%). Sixteen patients were admitted

TABLE 2 Comparison of severity according to CTCAE.

	Grade 3, *n* = 73 (73%)	Grade 4, *n* = 27 (27%)	*p* value
Age (years), mean (±SD)	64.5 (±14.1)	66.1 (±12.2)	0.69
Sex, *n* (%)			
Female	31 (42.5)	11 (40.7)	0.99
Male	42 (57.5)	16 (59.3)	
Medical history, *n* (%)			
Cirrhosis	3 (4.1)	1 (3.7)	0.99
Autoimmune disease	2 (2.8)	0	0.99
Anti-HBc IgG	5 (6.8)	1 (3.7)	0.64
Cancer, *n* (%)			
Lung	24 (32.9)	9 (33.3)	0.70
Melanoma	22 (30.1)	10 (37)	
Renal and urothelial	17 (23.3)	3 (11.2)	
Other cancers[a]	10 (13.7)	5 (18.5)	
Cancer stade, *n* (%)			
Stade III	10 (20.4)	4 (30.8)	0.47
Stade IV	39 (79.6)	9 (69.2)	0.47
Liver metastasis	4 (5.8)	3 (13)	0.36
Checkpoint inhibitor, *n* (%)			
Anti-PD1	46 (63)	18 (66.7)	0.63
Anti-PDL1	5 (6.9)	3 (11.1)	
Combotherapy with anti-CTLA4	22 (30.1)	6 (22.2)	
Cycles of ICI infusion, mean (±SD)	5.9 (±7.8)	6.3 (±6.0)	0.24
Time from last infusion until onset (days), mean (±SD)	26.6 (±31.5)	32.3 (±25.6)	0.06
Pattern, *n* (%)			
Cholestatic	26 (35.6)	13 (48.2)	0.18
Mixed	17 (23.3)	2 (7.4)	
Hepatocellular	30 (41.1)	12 (44.4)	
Autoantibodies			
ANA only	24 (32.9)	7 (26.9)	0.63
ASMA	3 (4.1)	2 (7.4)	0.71
Bile duct injury, *n* (%)	6 (8.2)	5 (18.5)	0.16
Liver biopsy, *n* (%)	23 (31.5)	14 (51.9)	0.10
Multiple irAEs, *n* (%)	27 (37)	13 (48.1)	0.47
Hospitalisation, *n* (%)	4 (5.5)	12 (44.4)	**<0.001**
MELD score, median (range)	7.8 (6–15)	11.6 (6–26)	**0.006**
DILI-N severity score, *n* (%)			
Non severe	71 (97.3)	15 (55.6)	**<0.001**
Severe	2 (2.7)	12 (44.4)	
DILI-IEWG severity score, *n* (%)			
Non severe	73 (100)	20 (74.1)	**<0.001**
Severe	0	7 (25.9)	
Hepatitis treatment, *n* (%)			
Both steroids and UDCA	17 (23.3)	9 (33.3)	0.32
Steroids only	37 (50.7)	10 (37)	0.32
UDCA only	8 (11)	7 (25.9)	0.11
No treatment	9 (12.3)	1 (3.7)	0.28
Second-line immunosuppressant	3 (4.1)	6 (22.2)	**0.01**
ICI rechallenge, *n* (%)	44 (61.1)	8 (30.8)	**0.02**
Response to cancer treatment (RECIST), *n* (%)			
Progressive disease	12 (16.4)	3 (11.1)	0.89
Stable disease	15 (20.5)	5 (18.5)	
Complete or partial response	38 (56.8)	14 (60.8)	
Days until hepatitis resolution, mean (±SD)	73.4 (±53.2)	67.8 (±38.1)	0.97

Abbreviations: ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; CTCAE, common Terminology Criteria for Adverse Events; DILI-IEWG, drug-induced liver injury International Working Group; DILI-N, drug-induced liver injury Network; ICI, immune checkpoint inhibitor; RECIST, response evaluation criteria in solid tumour; UDCA, ursodeoxycholic acid. Bold values are significant values.

[a]Head and neck cancer, hepatocellular carcinoma, colorectal cancer, oesophageal cancer, breast cancer, intestinal T-cell lymphoma.

to hospital (16%), including four patients requiring intensive care. Liver biopsy has been performed in 37 patients: 18 patients had microscopic biliary injury (48.6%), 5 patients had interface hepatitis (13.5%), and 5 patients had bridge necrosis (13.5%). Regarding hepatitis treatment, 75 patients received steroids (median RUCAM 8; IQR 2), 41 patients received UDCA (median RUCAM 8; IQR 2), 15 patients received UDCA only (median RUCAM 8; IQR 1.5), 10 patients had no treatment (median RUCAM 8; IQR 2.75), and 9 patients received second-line immunosuppressant (median RUCAM 7; IQR 2), mostly mycophenolate mofetil (MMF) (88.8%). The mean follow-up duration was 15.5 months.

3.2 | Severity classifications

When grading CHILI according to DILI-N and DILI-IEWG classifications, severe hepatitis was observed in 14% and 7%, respectively. No patients presented CHILI grade 5 according to DILI-N, nor grade 4 according to DILI-IEWG, as severity was assessed at onset. According to CTCAE classification, 73 patients were G3

TABLE 3 Comparison of severity according to DILI-N.

	Non severe, *n* = 86 (86%)	Severe, *n* = 14 (14%)	*p* value
Age (years), mean (±SD)	64.5 (±13.9)	67.4 (±10.4)	0.65
Sex, *n* (%)			
Female	36 (41.9)	6 (42.9)	0.99
Male	50 (58.1)	8 (57.1)	
Medical history, *n* (%)			
Cirrhosis	4 (4.7)	0	0.99
Autoimmune disease	2 (2.4)	0	0.99
Anti-HBc IgG	4 (4.7)	2 (14.3)	0.59
Cancer, *n* (%)			
Lung	31 (36.1)	2 (14.3)	0.31
Melanoma	26 (30.2)	6 (42.9)	
Renal and urothelial	18 (20.9)	2 (14.3)	
Other cancers[a]	11 (12.8)	4 (28.5)	
Cancer stade, *n* (%)			
Stade III	13 (15.1)	1 (7.1)	0.99
Stade IV	43 (50)	3 (21.4)	0.99
Liver metastasis	4 (4.7)	3 (21.4)	**0.04**
Checkpoint inhibitor, *n* (%)			
Anti-PD1	54 (62.8)	10 (71.4)	0.26
Anti-PDL1	6 (7)	2 (14.3)	
Combotherapy with anti-CTLA4	26 (30.2)	2 (14.3)	
Cycles of ICI infusion, mean (±SD)	6.4 (±7.8)	3.8 (±2.5)	0.42
Time from last infusion until onset (days), mean (±SD)	27.9 (±30.1)	30.6 (±30.5)	0.44
Pattern, *n* (%)			
Cholestatic	34 (39.5)	5 (35.7)	0.79
Mixed	17 (19.8)	2 (14.3)	
Hepatocellular	35 (40.7)	7 (50)	
Autoantibodies			
ANA only	27 (31.8)	4 (28.6)	0.99
ASMA	4 (4.7)	1 (7.1)	0.60
Bile duct injury, *n* (%)	10 (11.6)	1 (7.1)	0.99
Liver biopsy, *n* (%)	27 (31.4)	10 (71.4)	**0.006**
Multiple irAEs, *n* (%)	42 (42.4)	6 (40.0)	0.99
Hospitalisation, *n* (%)	2 (2.3)	14 (100)	**<0.001**
MELD score, median (range)	7.7 (6–15)	14.7 (7–26)	**<0.001**
CTCAE severity score, *n* (%)			
Grade 3	71 (82.6)	2 (14.3)	**<0.001**
Grade 4	15 (17.4)	12 (85.7)	
DILI-IEWG severity score, *n* (%)			
Non severe	86 (100)	7 (50)	**<0.001**
Severe	0	7 (50)	
Hepatitis treatment, *n* (%)			
Both steroids and UDCA	51 (59.3)	7 (46.7)	0.79
Steroids only	42 (48.8)	5 (35.7)	0.40
UDCA only	13 (15.1)	2 (14.3)	0.99
No treatment	15 (17.4)	0	0.21
Second-line immunosuppressant	4 (4.7)	4 (26.7)	**0.01**
ICI rechallenge, *n* (%)	51 (60)	1 (7.1)	**<0.001**
Response to cancer treatment (RECIST), n (%)			
Progressive disease	11 (13.3)	2 (18.2)	0.19
Stable disease	20 (24.1)	2 (18.2)	
Complete or partial response	61 (62.6)	7 (63.7)	
Days until hepatitis resolution, mean (±SD)	73.9 (±51.2)	51.5 (±32.7)	0.37

Abbreviations: ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; CTCAE, Common Terminology Criteria for Adverse Events; DILI-IEWG, drug-induced liver injury international working group; DILI-N, drug-induced liver injury network; ICI, immune checkpoint inhibitor; RECIST, response evaluation criteria in solid tumour; UDCA, ursodeoxycholic acid. Bold values are significant values.

[a]Head and neck cancer, hepatocellular carcinoma, colorectal cancer, oesophageal cancer, breast cancer, intestinal T-cell lymphoma.

and 27 patients were G4; Table 2 shows the comparison between these two grades. The median MELD score was 7[6–26] and was associated with each severity classification according to CTCAE, DILI-N and DILI-IEWG ($p < 0.001$ respectively). Liver biopsies were not significantly more frequent in CTCAE G4 hepatitis compared to G3 (51.9% vs. 31.5%; $p = 0.10$), but severe hepatitis according to DILI-N ($n = 10$, 71.4%, $p = 0.006$), and DILI-IEWG ($n = 6$, 85.7%; $p = 0.01$) were significantly more biopsied (Tables 3 and 4). Bridging necrosis was statistically associated with severe hepatitis according to DILI-N ($n = 3$, 21.4%; $p = 0.019$), and DILI-IEWG ($n = 3$, 50%; $p = 0.022$). There was no significant difference regarding the presence of multiple adverse events, autoimmune feature, history of liver disease, or response to cancer treatment, when comparing severity. Steroid administration and days until hepatitis resolution were not significantly increased in case of severe hepatitis, whatever the severity classification. ICI was significantly more likely to be resumed after CTCAE grade 3 hepatitis ($n = 44$, 61.1%; p = 0.02), and after non-severe hepatitis according to DILI-N ($n = 51$, 60%; $p < 0.001$) and DILI-IEWG ($n = 52$, 57.1%; $p = 0.004$). CHILI recurrence after re-challenging

TABLE 4 Comparison of severity according to DILI-IEWG.

	Non severe, $n=93$ (93%)	Severe, $n=7$ (7%)	p value
Age (years), mean (±SD)	64.5 (±13.6)	69.7 (±12.6)	0.37
Sex, *n* (%)			
Female	31 (42.5)	11 (40.7)	0.99
Male	42 (57.5)	16 (59.3)	
Cancer, *n* (%)			
Lung	32 (34.4)	1 (14.3)	0.50
Melanoma	29 (31.2)	3 (42.9)	
Renal and urothelial	19 (20.4)	1 (14.3)	
Other cancers[a]	13 (14)	2 (28.5)	
Cancer stade, *n* (%)			
Stade III	13 (14)	1 (14.3)	0.54
Stade IV	46 (49.5)	2 (28.6)	0.54
Liver metastasis	6 (6.5)	1 (14.3)	0.33
Checkpoint inhibitor, *n* (%)			
Anti-PD1	59 (63.4)	5 (71.4)	0.44
Anti-PDL1	7 (7.5)	1 (14.3)	
Combotherapy with anti-CTLA4	27 (29.1)	1 (14.3)	
Cycles of ICI infusion, mean (±SD)	6.2 (±7.5)	3.3 (±1.5)	0.69
Time until onset (days), mean (±SD)	29.2 (±31.1)	18.7 (±8.2)	0.62
Pattern, *n* (%)			
Cholestatic	38 (40.9)	1 (14.3)	0.08
Mixed	19 (20.4)	0	
Hepatocellular	36 (38.7)	6 (85.7)	
Autoantibodies			
ANA only	29 (31.5)	2 (28.6)	0.99
ASMA	5 (5.4)	0	0.99
Bile duct injury, *n* (%)	10 (10.8)	1 (14.3)	0.57
Liver biopsy, *n* (%)	31 (33.3)	6 (85.7)	**0.01**
Multiple irAEs, *n* (%)	37 (39.8)	3 (42.9)	0.99
Hospitalisation, *n* (%)	9 (9.7)	7 (100)	**<0.001**
MELD score, median (range)	7.9 (6–15)	18.6 (11–26)	**<0.001**
CTCAE severity score, *n* (%)			
Grade 3	73 (78.5)	0	**<0.001**
Grade 4	20 (21.5)	7 (100)	
DILI-N severity score, *n* (%)			
Non severe	86 (92.5)	0	**<0.001**
Severe	7 (7.5)	7 (100)	
Hepatitis treatment, *n* (%)			
Both steroids and UDCA	23 (24.7)	3 (42.9)	0.37
Steroids only	43 (46.2)	4 (57.1)	0.70
UDCA only	15 (16.1)	0	0.59
No treatment	10 (10.8)	0	0.99
Second-line immunosuppressant	5 (5.5)	4 (57.1)	**0.001**
ICI rechallenge, *n* (%)	52 (57.1)	0	**0.004**
Response to cancer treatment (RECIST), *n* (%)			
Progressive disease	15 (17.7)	0	0.68
Stable disease	19 (22.4)	1 (20)	
Complete or partial response	48 (56.4)	4 (57.1)	
Days until hepatitis resolution, mean (±SD)	55.7 (±42.5)	51 (±30.8)	*0.95*

Abbreviations: ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; CTCAE, Common Terminology Criteria for Adverse Events; DILI-IEWG, drug-induced liver injury international working group; DILI-N, drug-induced liver injury Network; ICI, immune checkpoint Inhibitor; RECIST, response evaluation criteria in solid tumour; UDCA, ursodeoxycholic acid. Bold values are significant values.

[a]Head and neck cancer, hepatocellular carcinoma, colorectal cancer, oesophageal cancer, breast cancer, intestinal T-cell lymphoma.

was not associated with the severity of initial CHILI, regardless of the severity classifications.

3.3 | Liver-related outcome: ALI

ALI occurred in seven patients (7%), among them 5 patients had hepatic encephalopathy (i.e. ALF). The characteristics of patients with ALI are summarised in Table S2: CHILI pattern was mostly hepatocellular ($n=5$), five patients developed ALF, and four patients received a second-line treatment with MMF. There was a difference regarding ALI between CTCAE G3 and G4 ($p=0.002$), and between non-severe and severe hepatitis according to DILI-N ($p<0.0001$) and DILI-IEWG ($p<0.0001$) (Figure 2). At 6 months, the ALI-free survival rates were 92.9% (95% CI: 59.1–99.0) for G3, and 40% (95% CI: 12.3–67.0) for G4 according to CTCAE (Figure 2A). According to DILI-N, the ALI-free survival rate at 6 months was 100% (95% CI: 100.0–100.0) for non-severe and 12.5% (95% CI: 0.7–42.3) for severe hepatitis (Figure 2B). In the DILI-IEWG, the 6-month ALI-free survival rate was 94.4% (95% CI: 66.6–99.2) for non-severe and 0.0% (95% CI: 0.0–0.0) for severe (Figure 2C). Hyperbilirubinemia was significantly associated with hospitalisation ($n=12$, 46.2%; $p<0.001$) and UDCA treatment ($n=16$, 61.5%; $p=0.03$). Jaundice was significantly associated with hepatic encephalopathy ($n=5$, 26.3%; $p<0.001$), second-line immunosuppressant therapy ($n=6$, 31.6%; $p=0.001$), plasmapheresis ($n=2$, 10.5%; $p=0.04$), and 3-months mortality ($n=3$, 15.8%; $p=0.006$). ALI and hyperbilirubinemia, including jaundice, were not significantly associated with any histological lesion.

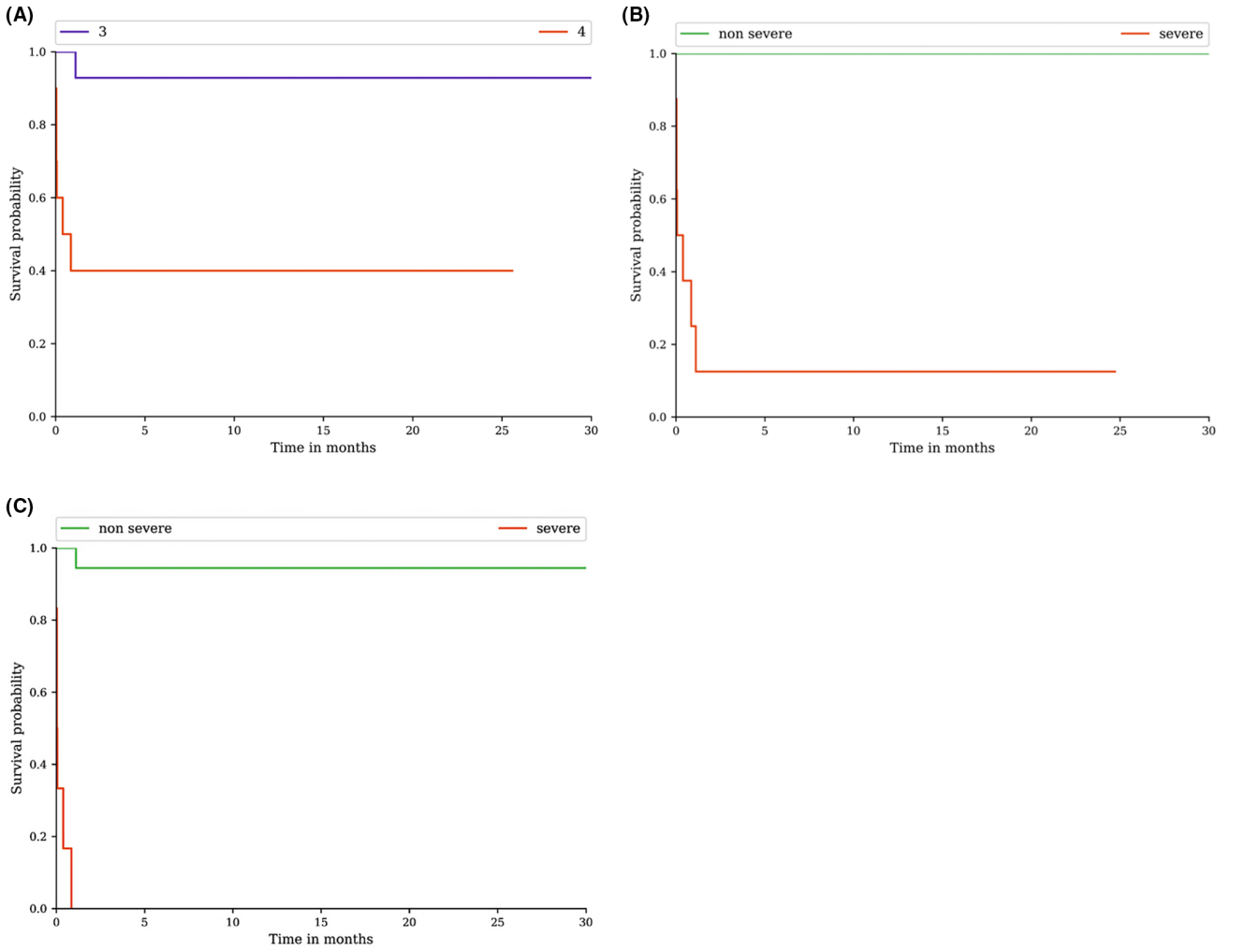

FIGURE 2 Acute liver injury estimated according to severity classifications CTCAE, DILI-N and DILI-IEWG. (A) Acute liver injury stratified by severity according to CTCAE: G3 vs. G4; $p=0.002$. (B) Acute liver injury stratified by severity according to DILI-N; $p<0.0001$. (C) Acute liver injury stratified by severity according to DILI-IEWG; $p<0.0001$. Acute liver injury rate was estimated using the Kaplan–Meier method and Cox test regression in percentage. Non severe is grades 1 and 2; Severe is grades 3 and 4.

3.4 | Secondary outcomes

Hospitalisation, hepatic encephalopathy, and second-line immunosuppressant were significantly associated with the severity according to CTCAE (Table 2), DILI-N (Table 3), and DILI-IEWG (Table 4). The median hospital stay was 7 days (2–83), and the median delay between onset of CHILI and initiation of second-line immunosuppressant was 27 days (8–483). Five patients had hepatic encephalopathy (5%), and lobular necrosis with bridge necrosis was significantly more frequent in those patients with hepatic encephalopathy ($n=2$, 66.7%; $p=0.04$). During the follow-up, 22 patients died (22%), mostly after neoplasia evolution ($n=19$, 86.4%), and three patients died from ALF (13.6%). Mortality at 3-months was significantly associated with ALI and hepatic encephalopathy ($n=3$, 100%; $p<0.001$). Severity grade according to CTCAE was not significantly associated with 3-months mortality (G3 1.4%, G4 7.7%; $p=0.17$), in contrast to DILI-N (G1 0%, G2 0%, G3 12.5%, G4 40%; $p=0.002$) and DILI-IEWG (G1 0%, G2 10%, G3 28.6%; p = 0.002). Overall mortality was not associated with severity according to CTCAE, DILI-N, nor DILI-IEWG.

3.5 | Severity classifications performance

Compared with CTCAE classification, the DILI-N and DILI-IEWG classifications had a better performance in predicting liver dysfunction in severe hepatitis ($p<0.05$) (Figure 3). The AUC difference between CTCAE classification and MELD score according to ALI was 0.09 ($p<0.01$, $z=2.81$). The area under the curve was 0.81 (95% CI: [0.67; 0.96]) for CTCAE to predict ALI, 0.90 (95% CI: [0.74; 1.06]) for MELD score, 0.98 (95% CI: [0.97; 1.0]) for DILI-N and 0.98 (95% CI: [0.96; 1.0]) for DILI-IEWG (Figure 3). The optimal cut-offs to predict ALI were grade 4 by CTCAE, 11-point threshold for MELD score, grade 3 by DILI-N, and grade 2 by DILI-IEWG. The area under the curve for total bilirubin to predict ALI was 0.79 (95% CI: [0.56; 1.0]),

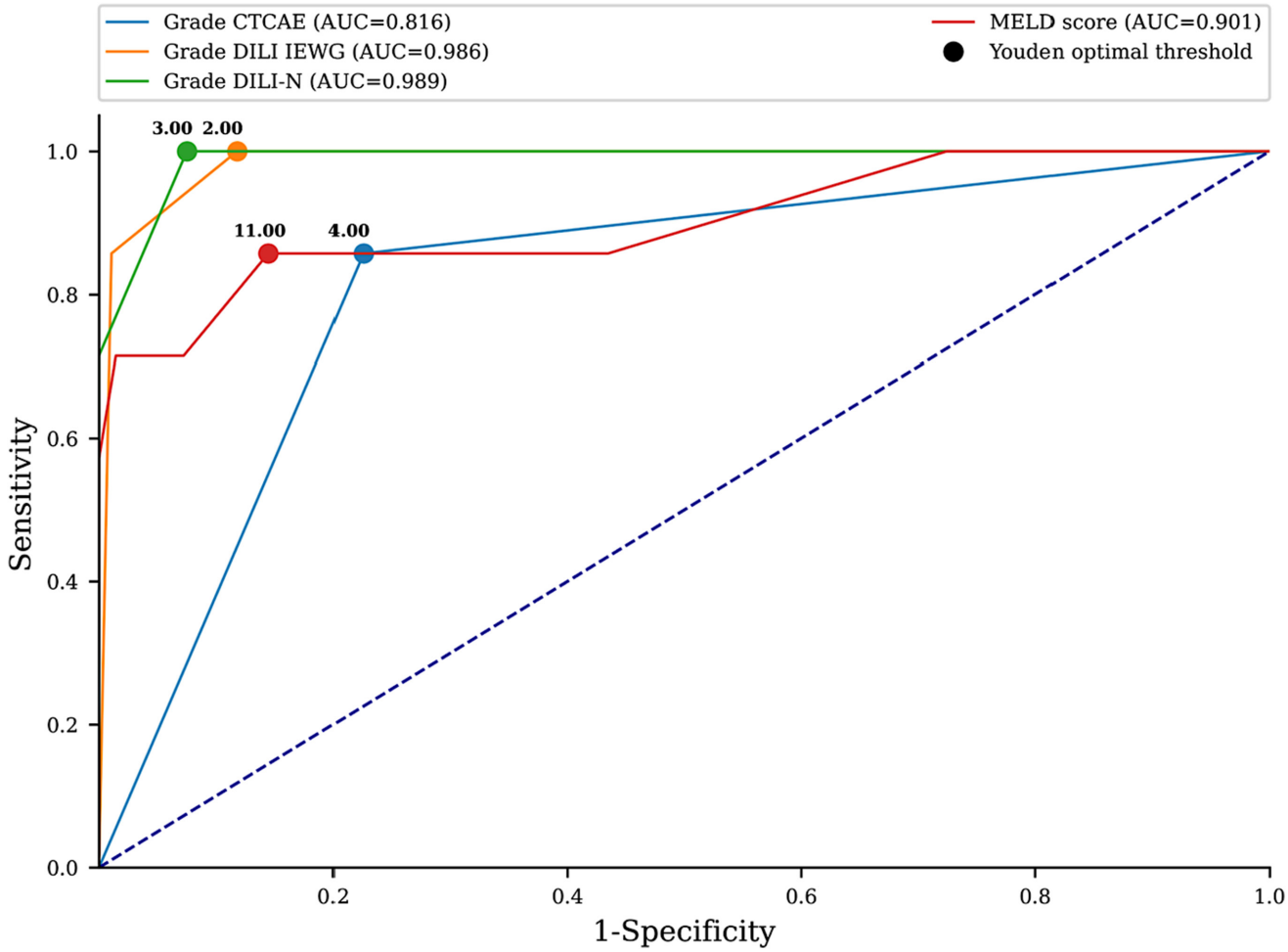

FIGURE 3 Correlation of severity classifications to predict acute liver injury. Graph shows receiver operating characteristic curve for predicting Acute Liver Injury. Solid blue line indicates Common Terminology Criteria for Adverse Events (CTCAE), solid red line indicates MELD (Model for End-stage Liver Disease), solid green line indicates DILI-N (Drug Induced Liver Injury-Network), and solid orange line indicates DILI-IEWG (Drug Induced Liver Injury-International Expert Working Group).

and the optimal cut-off value for total bilirubin to predict ALI was 31.2 μmol/L.

4 | DISCUSSION

This retrospective study included 100 patients with severe CHILI according to CTCAE and compared different validated severity classifications to assess liver outcomes. CHILI pattern was mostly hepatocellular, median RUCAM score was 8 and median MELD score was 7. According to the CTCAE classification, 27 patients had a life-threatening hepatitis, whereas only 14 patients and seven patients were severe according to DILI-N and DILI-IEWG classifications respectively. Although, the last CTCAE classification v5,[10] including total bilirubin, appears to accurately predict liver dysfunction accurately, but is insufficient in predicting 3-months mortality, contrary to DILI-N (23.1% vs. 0%, $p=0.002$) and DILI-IEWG (28.6% vs. 1.1%, $p=0.01$) classifications. Indeed, we found that the DILI classifications (DILI-N and DILI-IEWG) had a better performance liver dysfunction (respectively $p<0.05$), compared with the CTCAE classification. These findings show that the DILI classifications have a higher performance than the CTCAE classification in predicting ALI, ALF, and death at 3 months in patients with severe CHILI. Indeed, these results are consistent with a recent study by Atallah E et al who pointed out the discrepancy between the CTCAE classification and liver dysfunction,[7] with 99% of patients CTCAE grades 3 and 4, while no patient was DILI-IEWG severe. The same results were reported by Parlati L et al, who reported 86 severe CHILI according to CTCAE, with no patients developing liver failure.[23] Additionally, steroids remain the recommended first-line treatment for severe CHILI according to international recommendations,[9,11,26] but non-treated hepatitis seem to be correlated with non-severe CHILI according to DILI classifications in our study. Several studies have already reported cases with hepatitis grade ≥3 improvement without steroids, or with other therapeutics, such as UDCA.[27,28] Miller et al. had compared steroid-treated and untreated patients with CHILI, and found that patients on steroids took more time for hepatitis improvement compared to grade 1 (23 vs. 14 days, $p=0.043$).[26] Li et al.

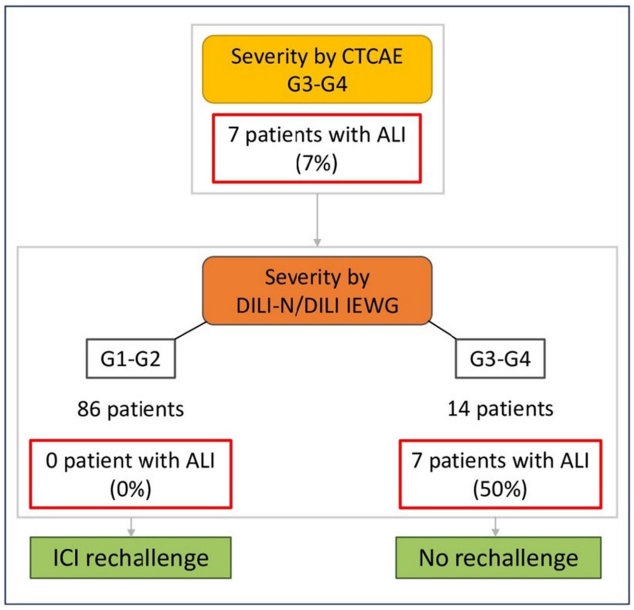

FIGURE 4 Proposed strategy for the management of patients with severe CHILI based on our results. Non severe is grades 1 and 2; Severe is grades 3 and 4. ALI, acute liver injury; CTCAE, Common Terminology Criteria for Adverse Events; DILI-IEWG, Drug Induced Liver Injury-International Expert Working Group; DILI-N, Drug Induced Liver Injury-Network.

also showed that high dose of steroids (≥1.5 mg/kg) did not impact the incidence of steroid-refractory hepatitis nor the time to ALT normalisation, compared to lower-dose regimen, but induced more steroid adverse events.[29] Recently, Riveiro-Barciela et al. proposed the use of corticosteroids depending on the degree of necroinflammation observed on liver biopsy.[30] Furthermore, we observed here a median delay of approximately 1 month before initiating a second-line immunosuppressant. This leads us to reconsider the definition of corticoresistance, which is defined as a lack of response to corticosteroid therapy after a 3-days period.[31] Still debating guidelines for the management of CHILI, ICI rechallenge after severe hepatitis is not recommended beyond CTCAE grade 3. Resuming ICI is an oncological challenge for patients with neoplasia, since patients experiencing irAEs often have partial or complete oncological response to ICIs. Several studies have already shown the feasibility of resuming ICI after grade ≥3 hepatitis, as there is no systematic recurrence, and the recurrent hepatitis is not worse.[27,32] Contraindications to the resumption of ICI might be reserved for patients with ALI. Finally, we propose in Figure 4 a strategy for the management of severe CHILI, to more clearly identify patients with severe hepatitis. Our statements regarding ICI rechallenge need more studies to be validated, but seem to challenge the over-restrictive guidelines, as continuing ICI may be the only life-prolonging option in CHILI patients with advanced neoplasia. Thus, there may be a bias in rechallenged patients as the most severe patients may be less likely to respond to corticosteroids and therefore less likely to be rechallenged. Further studies are needed to understand the mechanisms involved in the response to corticosteroid therapy in these patients. Our study has other limitations: (1) one patient had been transplanted but had discontinued immunosuppression therapy because of cancer, (2) six patients had possible causality grading assessed by the updated RUCAM, and (3) inclusion of patients from a special multidisciplinary meeting may have induced a selection bias. Beyond the limitations of the retrospective study design, we observed here a greater number of patients with ALI due to CHILI than in previous studies. Moreover, efficacy of the CTCAE was verified by cases assessed by the updated RUCAM, which helps to define characteristics of CHILI, not achieved by any other non-validated procedure. Also, the MELD score, which has been previously studied in DILI patients,[22,33] is very interesting in our CHILI population, since it also seems to correlate with severity above the threshold of 11. In conclusion, the CTCAE classification is associated with severity, but combining it with the DILI classifications is more specific for predicting ALI, and therefore helps to identify the patients most at risk of liver dysfunction and death at 3 months (Figure 4). This approach would permit the more effective selection of patients with severe conditions that may require the administration of IV corticosteroids or second-line immunosuppressant and avoid intensive treatment in non-severe patients. Prognostic classifications DILI-N and DILI-IEWG might still be validated and based on the validated RUCAM, and even more specific prognostic scoring systems, based on the validated updated RUCAM, might be interesting in CHILI. Further studies are needed to accurately predict the response to corticosteroids in severe CHILI patients. The insights of this study highlight that current management guidelines may require revision, because they are likely to result in the overtreatment of patients with CHILI and to limit the possibility of ICI rechallenge.

AUTHOR CONTRIBUTIONS

Lina Hountondji: Conceptualization; investigation; writing – original draft; methodology; visualization; data curation; formal analysis; project administration; resources; validation; writing – review and editing. **Stéphanie Faure:** Resources; validation; writing – review and editing. **Pascale Palassin:** Resources; visualization. **Philine Witkowski Durand Viel:** Resources. **Marie Dupuy:** Resources. **Dominique Larrey:** Resources. **Anouck Lamoureux:** Resources. **Cyrille Coustal:** Resources. **Dimitri Pureur:** Resources. **Candice Lesage:** Resources. **Éric Assenat:** Resources. **Benjamin Rivière:** Resources. **Jean-Luc Faillie:** Resources. **Xavier Quantin:** Resources. **Georges-Philippe Pageaux:** Validation; visualization; writing – review and editing. **Alexandre Thibault Jacques Maria:** Methodology; resources; validation; visualization; writing – original draft. **Lucy Meunier:** Conceptualization; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing; writing – original draft; formal analysis.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHORSHIP

Guarantor of the article: Lucy Meunier is the Guarantor of the article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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