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Operated Klatskin tumors: A series of 22 patients in a single center in Lebanon

Carine Korkmaz, Sami Choucair, Jihad Irani, Elias Saikaly, Ziad El Rassi

ABSTRACT

Aims: Klatskin tumors are the most common type of cholangiocarcinomas and they arise at the confluence of the bile ducts. The Bismuth classification divides them into four categories: I, II, IIIa/IIIb and IV. We retrospectively studied a series of 22 patients operated for Klatskin tumors and investigated the relation between clinicopathological features (size, extent of resection, bilirubin and prothrombine time (PT) levels, etc.), and outcome factors such as morbidity/mortality and recurrence. Methods: The hospital records were searched from 2001–2013 for operated Klatskin tumors. Five patients had types I/II and underwent resection of the bile ducts with regional lymphadenectomy, the remaining 17 patients had the same in addition to a right hepatectomy for type IIIa (8 patients), and a left hepatectomy for type IIIb (9 patients). Results: R0 resection rate was 91%. Bilirubin levels increased recurrence (p = 0.028). Decreased PT activity affected mortality (p = 0.019), and creatinine levels were found to increase mortality (p = 0.027) and diminish 1 and 3 year survival (p = 0.011, p = 0.027). Conclusion: R0 resection remains the most important factor to guide extent of surgery and to affect outcome. Bilirubin, PT and creatinine are valuable prognostic tools and "optimizing liver function" prior to surgery should be attempted. Further studies with a bigger sample are needed to better elucidate the effect of clinicopathological parameters on outcome.

Keywords: Hilar cholangiocarcinoma, Hepatectomy, Klatskin, Regional lymphadenectomy

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INTRODUCTION

Klatskin tumors are cholangiocarcinomas (CCA) that arise from hilar bile ducts and their confluence. Forty to sixty percent of CCAs are Klatskin tumors making them the most common type [1, 2]. The incidence of CCA is around 2 in 100,000 in the USA [1] and incidence in Lebanon and the Middle East is unknown. The presenting symptoms range from vague abdominal pain to weight loss, jaundice and pruritus depending on the level and degree of bile duct obstruction [3]. Diagnosing this tumor and classifying it requires multiples imaging modalities starting with the least invasive like ultrasound, Computed tomography (CT) scan and MRI scan, and often necessitates endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). Multiple classification systems exist like the American Joint Committee on Cancer (AJCC), the Bismuth-Corlette, the Memorial Sloan Kettering Cancer Center (MSKCC) and recently the International Cholangiocarcinoma Group Staging System [1, 3, 4–6] , the first one correlating poorly the type with the corresponding treatment.

The Bismuth classification divides Klatskin tumors into four categories according to the involvement of the bile ducts confluence and its extension to second order bile ducts: type I involves the common hepatic duct without reaching the confluence, type II reaches the confluence, types IIIa and IIIb reach the second order bile duct bifurcation on the right or left respectively, and type IV reaches both and is considered unresectable.

Medical literature has consistently demonstrated the importance and necessity of a negative margin resection (R0) for optimal chances of survival [1–3, 6–12]. While the latter remains the most important factor other parameters have been investigated for their effect on prognosis: extent of resection, bilirubin levels, underlying liver disorders, etc.

Our study examines a series of 22 patients operated for Klatskin tumors at our institution and investigates the association between clinicopathological features and selected postoperative outcomes namely survival, morbidity, mortality and recurrence.

MATERIALS AND METHODS

Patients

We retrospectively reviewed hospital records between 2001 and 2013 at our tertiary medical center in Beirut. Twenty-two patients with operated resectable Klatskin tumor were identified at our institution. The missing data was completed by looking at outpatient clinic records and by phone conversations with affected patients or their surrogates. The following cases were excluded: intrahepatic and distal CCAs, patients who were found inoperable during laparotomy or laparoscopy, in addition to two patients who had concomitant gallbladder cancer.

Classification and resectability

Tumors were classified according to the Bismuth-Corlette classification which was deduced from the preoperative imaging and modified according to the intraoperative findings by the operating surgeon. None of these patients underwent preoperative chemotherapy. Computed tomography scan was performed on all patients, in addition to ERCP or percutaneous transhepatic cholangiography (PTC) or both as needed, MRI-MRCP was done selectively to help determine the type and resectability and relation to blood vessels, and arteriogram was performed in one case only. Preoperative biliary drainage was performed at surgeon or oncologist's discretion, rather than based on a predetermined bilirubin cut-off.

All patients in our study were considered resectable according to the following criteria: no distant metastases, no type IV Klatskin, no invasion of the main portal vein or both of its branches, no contralateral involvement of the hepatic artery or the portal vein [1, 13].

The child score was mostly child A, or non-cirrhotic when the bilirubin levels were not markedly elevated.

None of the patients that remained after exclusion underwent staging laparoscopy. None had portal vein embolization preoperatively.

Surgical Technique

The surgery performed for types I and II consisted of: resection of the common bile duct (CBD) with the bile duct confluence, cholecystectomy and lymph node dissection of the hepatoduodenal ligament. The same was done for types IIIa and IIIb with the addition of a right or left hepatectomy accordingly; the hepatectomy was extended depending on tumor extension, in an effort to achieve R0 resection. No celiac or para-aortic lymph nodes were harvested. The caudate lobe was removed selectively when involved or in direct contact with the tumor [14]. Plasty of the bile ducts (L and R, or secondary branch bile ducts) was done when needed and when the remaining bile stumps could be anastomosed together [15], and in order to restore continuity with the gastrointestinal tract hepaticojejunostomy was done in single or multiple as needed in a Roux-en-Y fashion. The surgeries were performed by the same surgeon.

When vessels were involved, a vascular surgeon performed the repairs. The specimen was not routinely submitted to frozen section but rather at the surgeon discretion. Furthermore an additional margin resection was done when possible and when margins were positive.

Variables

We collected data on risk factors, and preoperative laboratory tests. Intraoperative mortality was defined as death on the operating table (no cases occurred in our series); early mortality was defined as death within 30 days of surgery. Morbidity is defined as any complication arising after surgery and considered related to it directly

(e.g., fistula) or indirectly (e.g., myocardial infarction); early morbidity (within 30 days of surgery) and late morbidity were grouped together for interpretation.

Statistical Analysis

In a first step, we described our patients' characteristics using traditional descriptive statistics: continuous variables were summarized using means, medians and standard deviation (ex: age, INR, creatinine, etc.). Categorical variables were summarized mainly by proportions and percentages (ex: sex, histology, mortality and morbidity at different times, etc.). In a second step, we looked for associations between independent variables (ex: age, sex, baseline tumor characteristics…) and outcomes of interest, in particular mortality at 1, 3 and 5 years, recurrence, and early complications. For this purpose, chi-square was used when the independent variable was categorical (or Fisher Exact test when appropriate), and student's t-test or its non-parametric equivalent when the independent variable was continuous. Survival analysis was done using Kaplan-Meier methods. p-value less than 0.05 were considered statistically significant. All statistical analysis was performed using SPSS V20.0

RESULTS

Out of 22 patients, fourteen were men and eight were women. The mean age was 60 (SD 15), and the most common type was Bismuth III (Table 1). Adjuvant chemotherapy was administered to four patients only according to oncologist's decision, the regimen was not always available in the records, and 3 (13.6%) patients had preoperative biliary drainage (PBD). R0 resection was achieved in 20 patients (91%) with the remaining two having an R1 resection (Table 1). Three patients died within 30 days of surgery; the causes were acute renal failure, ARDS, and hemorrhage. Median survival was 27 months (Table 2). Disease-free survival was 34 months calculated based on data of 15 patients because one was lost to follow-up and for the remaining six the records were missing the exact date of recurrence. The latter did not correlate to Klatskin type.

Of the patients who had an R1 resection, one died after 2 weeks in the hospital from acute renal failure and the other died after three years from recurrence.

At the time of the study, nine patients (41%) were still alive; the longest interval being 12 years, belonging to a patient who had Klatskin IIIb, negative lymph nodes, and involvement of both PV and HA; he was 69 at the time of his surgery.

Lymph nodes positivity was found in 9 (47%) patients, and in 3 pathology reports there were no sampled lymph nodes found (Table 1).

Bivariate analysis and survival analysis results are given in Tables 3 and 4. We found that decreased PT and elevated bilirubin, increased recurrence rates, and increased creatinine even when within normal limits, decreased 1- and 3-year survival.

We compared survival between types I/II and types IIIa/b, considering that the latter required more extensive surgery, and no significant difference was found (Figure 1). We also compared the right sided tumors (IIIa) to the left sided ones (IIIb) and Figure 2 shows almost identical survival curves.

Table 1: Demographic and clinical covariates of the study cohort

	n (%)
Age (years)*	60 ± 15*
Sex (Male)	14 (64)
Bismuth-Corlette	
I	1 (4.5)
II	4 (18.2)
IIIA	8 (36.4)
IIIB	9 (40.9)
R0 status	20 (91)
Size (cm)*	3.85 ± 2.03*
No. of patients with + lymph nodes	9 (47.4)
Preoperative biliary drainage	3 (13.6)
Differentiation	
Well differentiated	6 (27.3)
Mod differentiated	14 (63.6)
Poorly differentiated	2 (9.1)

* Data reported as mean ± SD

Table 2: Outcome of different parameters observed in the study

	n (%)
Morbidity (n = 22)	10 (45.5)
Recurrence (n = 18)	7 (38.9)
Median survival in months	27 (35) *
Disease-free survival in m (n = 15)	34
1 year (n = 21)	18 (85.7)
3 years (n = 18)	9 (50)
5 years (n = 17)	4 (23.5)

* Data reported as median (mean). Disease-free survival is reported in months as the mean n = 15. Survival at 1 year: n = 21; 1 patient not applicable (less than 1 year post resection). At 3 years: n = 18; 3 patients not applicable, 1 lost to follow-up. At 5 years: n = 17; 4 not applicable, 1 lost to follow-up.

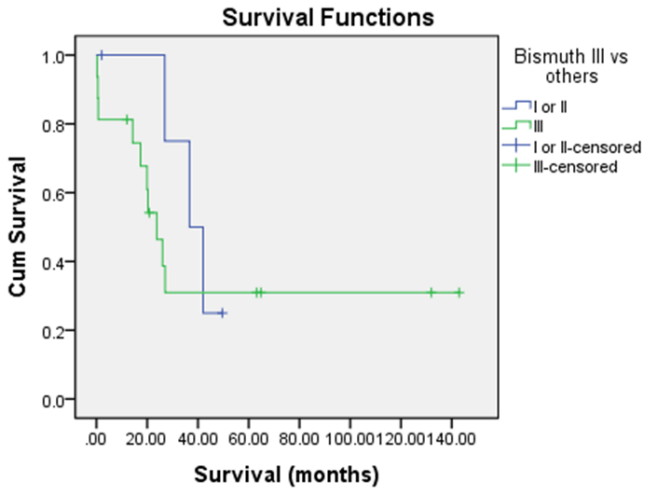

Figure 1: Kaplan–Meier survival curves showing patients with Bismuth types I & II (blue line) and patients with Bismuth type III (green line). Log Rank test p = 0.358

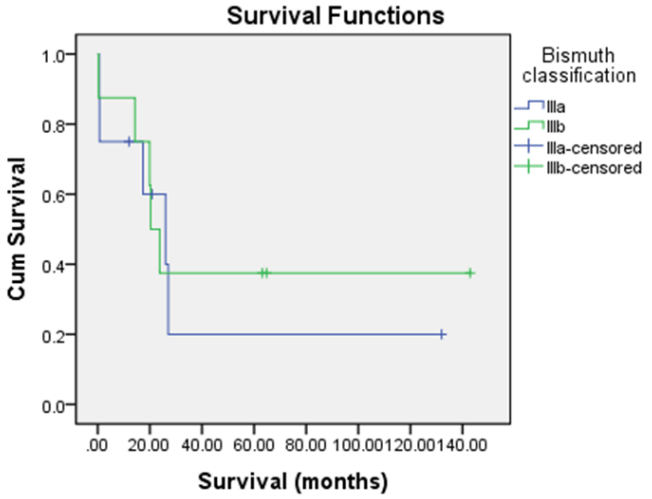

Figure 2: Kaplan–Meier survival curves showing patients with Bismuth type IIIa (blue line) and patients with Bismuth type IIIb (green line). Log Rank test p = 0.0802

Table 3: Qualitative risk factors correlated with morbidity, mortality, recurrence and at 1, 3 and 5 years.

	Patient n (%)	Morbidity %	Mortality %	Recurrence (%)	Survival in months 1 year (%)	3 year (%)	5 year (%)
Sex							
Male	14 (64)	50	64.3	41.7	84.6	54.5	18.2
vs. Female	8 (36)	37.5	57.1	33.3	87.5	42.9	33.3
		p= 0.675	p= 1.00	p= 1.00	p= 1.00	p= 1.00	p= 0.584
Bismuth I&II vs III							
I&II	5 (22.7)	40	60	60	100	100	0
III	17 (77.3)	47.1	62.5	30.8	82.4	35.7	28.6
		p= 1.00	p= 1.00	p= 0.326	p= 1.00	p= 0.082	p= 0.541
Bismuth IIIA vs IIIB							
IIIa	8 (36.4)	50	62.5	33.3	75	33.3	16.7
IIIb	9 (40.9)	44.4	62.5	28.6	88.9	37.5	37.5
		p= 1.00	p= 1.00	p= 1.00	p= 0.576	p= 1.00	p= 0.58
Stones							
Yes	6 (27.3)	50	100	75	66.7	33.3	0
No	16 (72.7)	43.8	46.7	28.6	93.3	58.3	36.4
		p= 1.00	p= 0.046 *	p= 0.245	p= 0.184	p= 0.62	p= 0.237
PV invasion							
Yes	4 (18.2)	100	25	0	75	50	50
No	18 (81.8)	33.3	70.6	46.7	88.2	50	20
		p= 0.029 *	p= 0.253	p= 0.245	p= 0.489	p= 1.00	p= 0.426
Perineural infiltration							
Yes	17 (77.3)	41.2	64.7	35.7	81.2	40	21.4
No	5 (22.7)	60	50	50	100	100	33.3
		p= 0.624	p= 0.618	p= 1.00	p= 0.549	p= 0.206	p= 1.00
Differentiation							
Well diff	6 (27.3)	33.3	50	20	83.3	50	50
Mod/Poorly diff	16 (72.7)	50	66.7	46.2	86.7	50	9.1
		p= 0.646	p= 0.631	p= 0.596	p= 1.00	p= 1.00	p= 0.099
LN pos							
Yes	9 (47.4)	11.1	55.6	22.2	100	57.1	28.6
No	10 (52.6)	70	55.6	42.9	80	62.5	28.6
		p= 0.02 *	p= 1.00	p= 0.596	p= 0.477	p= 1.00	p= 1.00
Caud. Lobe removal							
Yes	9 (41%)	44.4	100	71.4	89	25	0
No	13 (59%)	46.2	38.5	18.2	83.3	70	44.4
		p= 1.00	p= 0.007 *	p= 0.049 *	p= 1.00	p= 0.153	p= 0.082

Table 4: Quantitative risk factors correlated with morbidity, mortality, recurrence and survival at 1, 3 & 5 years.

	Morbidity		Mortality		Recurrence		1-yr survival		3-yr survival		5-yr survival	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Age	62.4 ± 10.7	58.3 ± 19 p= 0.541	63.3 ± 15.8	56 ± 16.5 p= 0.324	64.7 ± 17.9	55.9 ± 15.8 p= 0.289	58.2 ± 16.4	67.67 ± 11 p= 0.353	56.7 ± 19.5	65 ± 12.2 p= 0.292	52 ± 19.5	63.3 ± 15.8 p= 0.252
WBC	10.3 ± 4.8	10.2 ± 3.0 p= 0.945	9.5 ± 3.4	11.6 ± 4.6 p= 0.225	9.26 ± 3.99	10.9 ± 3.7 p= 0.373	10.1 ± 3.7	10.4 ± 5.6 p= 0.921	9.8 ± 3.8	10.0 ± 3.7 p= 0.887	9.7 ± 3.9	9.5 ± 3.4 p= 0.909
Total Bil	11.6 ± 8.2	7.7 ± 6.6 p= 0.277	9.2 ± 7.9	9.6 ± 7.8 p= 0.924	14.5 ± 7.0	6.3 ± 5.3 p= 0.028 *	9.6 ± 7.2	9.7 ± 12.3 p= 0.984	10.3 ± 8.4	7.8 ± 8.2 p= 0.587	5.1 ± 5.7	9.2 ± 7.9 p= 0.428
Cre	0.8 ± 0.3	0.9 ± 0.2 p= 0.883	0.97 ± 0.25	0.72 ± 0.2 p= 0.027 *	0.76 ± 0.2	0.76 ± 0.2 p= 0.115	0.84 ± 0.2	1.20 ± 0.4 p= 0.011 *	0.76 ± 0.2	1.03 ± 0.3 p= 0.027 *	0.70 ± 0.22	0.97 ± 0.25 p= 0.076
PT	84.2 ± 15.0	83.0 ± 14.3 p= 0.863	81.4 ± 11.3	73.8 ± 15.9 p= 0.019 *	88.0 ± 18.5	77.6 ± 11.7 p= 0.014 *	82.6 ± 16.8	90.3 ± 7.1 p= 0.689	76.7 ± 18.7	90.4 ± 9.1 p= 0.2	78.0 ± 18.2	88.2 ± 11.3 p= 0.239
INR	1.08 ± 0.17	1.11 ± 0.12 p= 0.349	1.05 ± 0.11	1.19 ± 0.18 p= 0.056	1.07 ± 0.19	1.15 ± 0.11 p= 0.055	1.11 ± 0.15	1.00 ± 0.08 p= 0.216	1.1 ± 0.13	1.0 ± 0.08 p= 0.2	1.1 ± 0.15	1.0 ± 0.09 p= 0.611
Size	4.0 ± 2.2	3.7 ± 2.0 p= 0.725	3.7 ± 1.9	4.2 ± 2.3 p= 0.63	3.8 ± 2.0	4.1 ± 2.3 p= 0.755	3.9 ± 2.2	3.5 ± 1.8 p= 0.756	4.3 ± 2.7	3.7 ± 1.8 p= 0.598	4.6 ± 3.4	3.7 ± 1.9 p= 0.54

DISCUSSION

The mean age of 60 in our study is similar to previous studies especially those conducted in Iran and Greece [16–18]. The early mortality was 13.6% and morbidity was 45%, the median survival was 27 months. Thirteen patients died at the time of the study, 8 were still alive and one was lost to follow-up. The one-year, three-year and five-year survival were 86%, 50% and 23% respectively (Table 2). These results are comparable to those registered in large center studies [1, 10, 14, 15, 18, 19]. Twenty patients (91%) had an R0 resection, this number is higher than most recorded for Klatskin, and this is partly due to our highly selective resectability criteria especially concerning those tumors which are between III and IV on imaging.

Age, gender, tumor size, differentiation level, perineural infiltration, lymph nodes positivity and ratio, adjuvant chemotherapy and preoperative biliary drainage did not affect outcome (Tables 3 and 4) [20]. We view this data as an underlining of the fact that R0 resection remains the most important factor to influence prognosis [1, 2, 12, 14, 21, 22].

Portal vein involvement and repair increased the incidence of perioperative complications but no effect was seen on mortality; in addition the longest survival interval recorded in our series belongs to a 69-year-old patient who had concomitant HA and PV repair. In review, Ito et al. show that portal vein resection does not affect mortality in most series but its long-term effect needs to be studied; most studies corroborate this finding when PVR is performed in centers with higher experience [22–26].

In our study, the caudate lobe was removed in nine patients (Table 3). The decision to remove it was made intraoperatively according to local advancement of the tumor in an aim to achieve clear margins rather than a standardized surgical technique. Of those nine patients, eight were undergoing a left hepatectomy for IIIb tumors and one was a Klatskin II [1, 7, 9, 14, 21, 27, 28]. The rate of caudate involvement in literature is between 40 and 98%, and its removal decreases local recurrence and increases five-year survival. There is no consensus on the necessity of removing it routinely: Brown [1] and AZ Kahn [7] advocate its routine removal when performing hepatectomy be it right or left [1] whereas Jarnagin and Shoup [27] recommend removing it when the tumor is left-sided [5, 27]. The latter correlates more with the practice in our institution where 8/9 of the Klatskin IIIb had caudate lobe removal. However, in our study the effect of segment I removal was a contradictory increase in overall mortality and recurrence rates; and one interpretation of this is that caudate lobe removal creates a selection bias to more advanced tumors.

The recurrence rate was increased by increased bilirubin and decreased PT. The prothrombine time (PT) also had an effect on overall mortality as well as creatinine. The effect of the latter was translated into a decrease in one year and three year survival rates (Table 4). We analyze these laboratory values together because they all reflect liver function, and "optimizing liver status" prior to surgery was proven beneficial by Ratti et al. [29]. High bilirubin levels are the result of obstructed bile ducts, and have consistently shown an increase in mortality through literature [2, 7, 15, 30]; O Farges [31] found a cut-off of 50 mmol/L above which bilirubin levels are deleterious, and Kahn et al. [7] recommends the normalization of bilirubin to 2 mg/dL prior to surgery to gain a positive effect on survival [30]. The non-normalization of bilirubin may be interpreted as advanced disease or irreversible liver damage and in both cases portends a worse prognosis. The way to normalize bilirubin levels is by performing preoperative biliary drainage (PBD). In our series, PBD was done in three patients (two of which were IIIa and the last was IIIb) based on surgeon judgment and it was not seen to affect morbidity or mortality [7, 29, 31–34]. In their series on Klatskin 3 and 4, Baton et al. [15] describe that at their institution PBD was done on the future liver remnant (FLR) when indicated by hepatic dysfunction, deterioration of performance status or impaired kidney function and it did not affect outcome [15]. O Farges et al. [31], in their study showed that when performed on the R hemiliver PBD decreased mortality and when done on L hemiliver PBD increased the mortality, this was explained by the causes of death: for R liver it was liver insufficiency and for L liver it was sepsis [31]. There seems to be consensus regarding the recommended use of PBD prior to portal vein embolization (PVE) [1, 12, 29, 32, 33]. Although in Japan and Asia, PBD is favored and recommended, as stated by Zhimin et al. [12], in western countries it is still done selectively and mainly on the FLR side, especially when tumor is IIIa or IV [12, 14, 30, 32, 33]. The main reason for this selectivity is that PBD is not without risks and drawbacks since it can reverse the natural atrophy of the hemiliver to be removed [1]. Perhaps in our institution the rate of preoperative biliary drainage could be increased and criteria developed for its use based on hepatic and kidney function.

The presence of gallstones had a significant effect on overall mortality and the clinical significance of this is yet to be determined (Table 3).

Adjuvant therapy did not affect outcome and this is consistent with most literature [1, 6, 14, 27].

No difference in outcome variables was noted between different Klatskin types as previously reported in the literature [4, 6, 8]. In Figures 1 and 2, we find no difference in overall survival between Klatskin types: I and II versus III (Figure 1) and IIIa versus IIIb (Figure 2). This may be due to the small sample size; tumor stage types IIIa and IIIb are expected to have slightly worse outcome than earlier types due to the advanced nature of the tumor into the liver and the more extensive surgery needed for cure.

Limitations

Our study is a case series and has its own limitations: The main one is the small sample size which renders analysis of data correlation less statistically significant.

The disease-free survival given includes 15 patients out of 22 because the exact date of recurrence was not always available in the records which were not computerized; the blood loss and operation time were not included in the examined parameters; the regimen of adjuvant chemotherapy was not available; the lymph node number is very variable across the patients with some having none harvested and some having up to 22 lymph nodes harvested; the creatinine clearance is not examined, neither are tumor markers nor liver enzymes. We did not use the AJCC staging system or MSKCC or the international staging system. Finally, morbidity was not studied according to the Clavien-Dindo classification.

CONCLUSION

In conclusion, Klatskin tumors are rare and there is ongoing discussion about their management and the ideal staging system. We present our center's experience in Beirut with a literature review and draw some conclusions: "ultimately what is important is not staging but resectability" as stated by A Z Khan and R0 resection remains the most important factor by far: even alone it can result in excellent survival. Preoperative biliary drainage could be a valuable tool when used selectively; we recommend its use on the future liver remnant when bilirubin and PT are elevated, mainly to optimize liver function and creatinine values. The exact cut-off values need to be elucidated in future trials as well as the role of creatinine clearance as a prognostic tool, and these parameters merit to be studied in a bigger sample study in order to improve statistical significance.

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Author Contributions

Carine Korkmaz – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Sami Choucair – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Jihad Irani – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Elias Saikaly – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ziad El Rassi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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