RESEARCH ARTICLE

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Comparison between Trans-Arterial Chemoembolization Followed by Stereotactic Body Radiation Rherapy and Trans-Arterial Chemoembolization Alone in BCLC Stage B Hepatocellular Carcinoma: A Pilot Study

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Abstract

Objective: Both Stereotactic Body Radiation Therapy (SBRT) and Trans-arterial Chemoembolization (TACE) are now being widely used to treat advanced hepatocellular carcinoma (HCC) and can improve tumor local control rates. We aimed at evaluating the efficacy and toxicity of combining SBRT and TACE in comparison to TACE alone in unresectable HCC. **Methods:** 42 unresectable Barcelona Clinic Liver Cancer (BCLC) stage B HCC Child Pugh (CP) A patients were randomized to receive either: TACE alone (Arm A) or TACE followed by SBRT (Arm B). Dose prescribed was 40Gy in 5consecutive daily fractions over 1 week . We compared the local control (LC), Progression free survival (PFS), overall survival (OS) and toxicity between the two arms. **Results:** 22 patients were in arm A versus 20 patients in arm B with median follow up 20 months starting recruitment from April 2021 till January 2023. Both LC, PFS were significantly better in Arm B. Complete remission (CR) rate was 54.5% and 75% in Arm A and B, respectively. Median PFS was 16 months in Arm B compared to 11 months in Arm A (p =0.003). Median OS was not reached in both arms. Both arms had comparable toxicities. **Conclusion:** Adding SBRT to TACE in advanced HCC, is safe and feasible with better efficacy in terms of LC and PFS with comparable side effects, in comparison to TACE alone.

Keywords: Transarterial chemoembolization (TACE)- Stereotactic Body Radiation therapy(SBRT)

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is a worldwide universal problem HCC is regarded as a serious public health problem in Egypt, where it accounts for 33.63 % of all malignancies in men and 13.54% in women [1].

A multidisciplinary team is essential to determining the therapeutic options and the overall prognosis of the disease, depending on certain features of tumor, such as size and local extent, and the patient's features, such as performance status, liver condition, and presence of extrahepatic spread, and based on the treatment intent, such as bridge-to-transplant, down staging to transplant, definitive/curative intent, or palliation [2][Honda, 2014 #10592].

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, trans arterial chemoembolization (TACE) is the first-line treatment for patients with intermediate-stage HCC with multinodular diasease (≥4 liver nodules) and well-preserved liver function with no evidence of vascular invasion or extra-hepatic spread. TACE alone rarely produces a complete response, which is attributed to the presence of remaining, viable tumor cells [3].

For individuals with incurable HCC, stereotactic body radiation therapy (SBRT) is another quickly developing treatment option. When high doses of radiation are precisely targeted at lesions, SBRT causes tumor necrosis. Its application is growing not only in early-stage HCC but also in portal vein or inferior vena cava thrombi, extending its use to pre-transplantation and the treatment of oligometastases. Nevertheless, SBRT is still considered a stand-in for traditional bridging therapies like TACE and radiofrequency ablation (RFA) [4].

When treating a lesion locally, combining TACE with SBRT can have a number of benefits. Delivering TACE first may cause the tumor to shrink, which will ultimately lead to a reduced SBRT volume and less toxicity. As a part of TACE, chemotherapy may serve as a radiosensitizer, amplifying the effects of radiation; however, tumor hypoxia brought on by embolization may offset this. In

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SBRT, lipiodol deposited during the embolization process can act as a landmark for tumor delineation guidance, potentially eliminating the need for fiducial marker insertion [3].

Over the past two decades, a greater understanding of the dose-volume effects of partial-liver radiotherapy has enabled radiation oncologists to predict the risk of radiation-induced liver disease (RILD) associated with a given treatment plan using normal tissue complication probability models [5]. Several prospective and retrospective studies have shown significant improvements regarding treatment response, local control (LC), progression-free survival (PFS), and overall survival (OS) with the addition of SBRT to TACE, compared to TACE alone, especially if the lesion size exceeded 3 cm [4].

Due to the lack of a successful treatment for RILD, this condition significantly restricts the use of SBRT. RILD is more likely to develop in Child Pugh (CP) class B than in class A patients [5, 6]. The place of SBRT in the therapeutic guidelines for unresectable HCC not eligible for transplant or local thermal ablation is uncertain. In this study, we hypothesized that adding SBRT to TACE can increase local control and hence, PFS in patients with unresectable BCLC stage B HCC. CP class A patients were selected to avoid the risk of developing RILD. Our aim was to find a new place for SBRT in the treatment algorithms, by exploring the efficacy and toxicity of combining it with TACE.

Materials and Methods

This is a pilot study that was carried out at the Clinical Oncology and Interventional Radiology Departments Cairo university during the period between April 2021 and January 2023. Forty-two consecutive patients diagnosed with Child A, BCLC Stage B HCC, with ≤3 HCC nodules, each up to 50 mm in diameter without vascular invasion, and inoperable because of poor general condition, surgery refusal, or unsuitability for radiofrequency ablation, were randomized to both treatment arms. This criteria does not fall completely in BCLC Stage B since we had a tight selection criteria fearing liver toxicity especially that liver cirrhosis on top of viral hepatitis is endemic in Egypt

Arm A included 22 patients treated by TACE only, and Arm B included 20 patients treated by TACE followed by SBRT. SBRT was started 1 month after the end of TACE. A written consent was obtained from each patient before recruitment fovr the study.

Transarterial Chemoembolization (TACE)

Using the Seldinger technique, a French catheter (4F to 5F) was inserted into the abdominal aorta through the right femoral artery. To determine the location of the tumor, hepatic artery selective arteriography was performed. To find any tumor staining in the remaining liver, hepatic angiography was performed. Next, through the catheter, an emulsion containing lipiodol (2–15 ml) and cisplatin (20–100 mg) was administered.

Stereotactic Body Radiation Therapy (SBRT)
Radiotherapy technique

Using a wing board, patients were immobilized in the supine position. Each patient underwent an inspiratory breath hold technique-assisted computed tomography (CT) scan with a 2 mm slice thickness and intravenous contrast administered. After then, all imaging serieswere moved to the treatment planning system (TPS).

The gross tumor volume (GTV) was delineated and guided by the available diagnostic imaging modality (MRI, triphasic CT or PET scan), and the tumor location was guided by the lipidol dye in the chemo-embolized lesion. A margin of 0.5 cm of planning tumor volume (PTV) was taken around the GTV with no Clinical Target volume (CTV)

Organs at risk (OAR) were contoured, including the spinal cord, remaining normal liver, kidneys, stomach, lungs, adjacent ribs, skin, heart, and great vessels. Eclipse TPS version 16.01.04 was used in the planning calculations. Patients were planned by volumetric modulated arc therapy (VMAT), and dose- volume histogram (DVH) was used to calculate the normal tissue dose distribution respecting the OAR tolerance doses (Table 1). The total dose prescribed was 40Gy/5fr/1w with a dose of 8Gy per fraction with biological effective dose (BED) 88Gy. Prescribed isodose coverage is at least 95% of the PTV received the prescribed dose.

Cone beam computed tomography (CBCT) was done on the machine daily prior to the start of each session to ensure proper positioning of the patients. Radiotherapy sessions were delivered on "UNIQUE" Varian machine.

Follow up and assessment of response

Performance status, history, physical examination, complete blood count, liver function tests, coagulation profile, electrolytes, and CP score were reassessed weekly during the first month after completion of the treatment course and then every three months.

Assessment was requested after one month and then every three months, consisting of triphasic CT abdomen and pelvis or PET/CT scan, liver function tests, and alfa-fetoprotein (AFP), following the end of either TACE (Arm A) or SBRT (Arm B), and radiological response to treatment was assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST criteria) [6]

Assessment of toxicity

Classic RILD is characterized by sub-acute liver toxicity, usually occurring 4–8 weeks after completion of radiation therapy, and is associated with hepatomegaly, anicteric ascites, and high alkaline phosphatase levels. Elevated liver enzymes greater than five times the high normal limit or a two-point or greater decline in the CP score were considered non-classic RILD [6].

Statistical analysis

Statistical analysis was conducted using SPSS 22nd edition; categorical variables were presented in frequency and percentages, and compared using Fisher exact test or Pearson chi2 test based on the rule of <20% of the cells

have a count <5. Quantitative variables were presented in mean, standard deviation, and range. A comparison of continuous variables was conducted using the student T test for normally distributed data and Mann-Whitney U test for non-parametric variables. Any p value <0.05 was considered significant.

Survival analysis was conducted to assess PFS between the studied groups, and the Kaplan Meier curve was used to visualize the survival difference between the studied groups. A log rank test was used to detect the significant difference in PFS among the studied groups and to assess PFS differences according to site and extent of relapse.

Results

The study included 42 patients, of whom 22 received TACE only (ARM A) and 20 underwent TACE followed by SBRT (ARM B). The median age of all patients was 59 years old, with range of (48-70). Most of the cases were males (>70%). The median follow up period was twenty months. The two patient groups' patient characteristics and those of the disease were equally distributed (Table 2).

Assessment of response

In arm A, patients' complete response (CR) was achieved in 54.5%, and partial response (PR) was 36.4%. and the rest had stationary disease (SD) (9.1%). In arm B, 75% of the group achieved CR, 15% achieved PR, and 7% achieved SD, i.e., there is an improvement of 25% in the CR rate in arm B, compared to arm A (Table 3). Mean AFP 1 month after the end of SBRT showed a significant marked decrease in arm B 18.4 ng/ml versus 176.5 ng/ml in arm A with a p value of 0.003.

Assessment of toxicities

In terms of post-SBRT liver-induced toxicity, there was a transient deterioration in liver functions 1 month after the end of the radiation therapy in 7 patients. However, most of them recovered within 3 months, with non-statistically significant deterioration from CP class A to B in arm B accounting for 10% versus 4.54% in the control

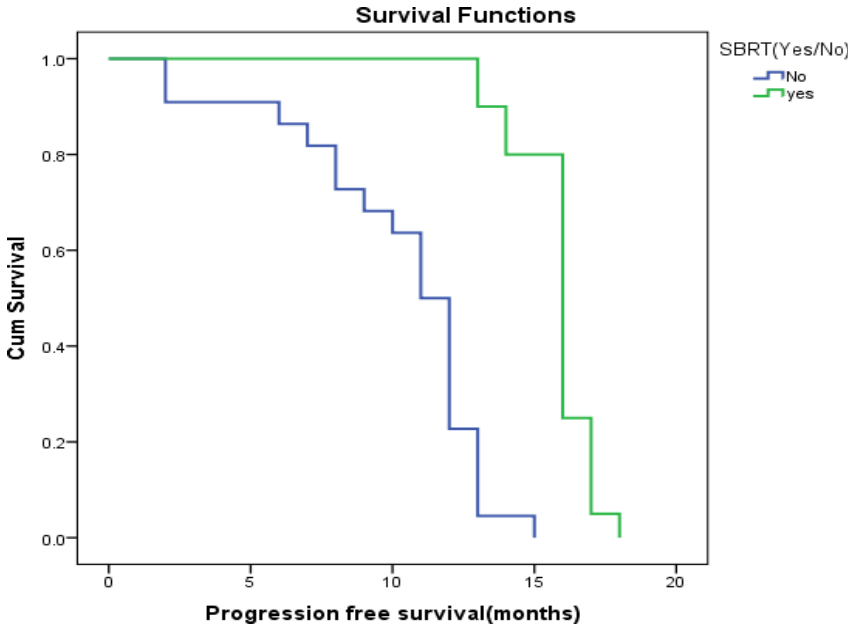

Figure 1. Kaplan Meier Curve Showing Progression Free Survival among Studied Groups.

Table 1. Dose Constraints for Organs at Risk for 5 Fractions Adapted from RTOG 1112 Protocl

Organ	Volume	Dose	Endpoint (> Grade 3)
Spinal cord	D_{max}	<25 Gy	Myelitis
Lung	10%	7Gy	Pneumonitis
Great vessels	<0.5cc	60Gy	Aneurysm
Rib	<1cc	16Gy	Pain or fracture
Heart	D_{max}	<27 Gy	Pericarditis
Skin	<10cc	16Gy	Ulceration
Stomach	<5cc	25 Gy	Ulceration
Normal liver (Liver minus	V_{10Gy}	<70% 18Gy	Radiation induced liver disease
GTV)	Mean liver dose	<700ml	
	V_{15Gy}		
Small bowel	<5cc	<25Gy	Grade 3 Enteritis
Kidney	Mean Kidney dose	<10Gy	Grade 3 Renal dysfunction

Table 2. Patients and Disease Characteristics of the Studied Groups

		Arm A		Arm B		
		Mean± SD	Range	Mean± SD	Range	P value
Age in years		60.2± 8.3	49-80	58.1± 8	48-70	0.394
		N	%			
Gender	Male	16	72.70%	15	75%	0.867
	Female	6	27.30%	5	25%	
ECOG performance status	1	16	72.70%	14	70%	0.845
	2	6	27.30%	6	30%	
Hypertension	No	16	72.70%	17	85%	0.333
	Yes	6	27.30%	3	15%	
Diabetes	No	15	68.20%	10	50%	0.231
	Yes	7	31.80%	10	50%	
Hepatitis C virus	No	3	13.60%	5	25%	0.349
	Yes	19	86.40%	15	75%	
CHILD status	A	22	100%	20	100%	0.945
Extent of disease	Bilobar	9	40.90%	7	35%	0.694
	Unilobular	13	59.10%	13	65%	
Degree of liver cirrhosis	Cirrhosis	21	95.50%	15	75%	0.098
	not known	1	4.50%	5	25%	
Baseline number of lesions	1	12	54.50%	12	60%	0.487
	2	10	45.50%	7	35%	
	3	0	0.00%	1	5%	
	Mean± SD		Range	Mean± SD	Range	
Baseline size of lesion (cm)			4.4± 0.9	3-6.5	4.9± 1.1	3.6-7

group with a p value of 0.181. In arm B, only two (10%) patients developed radiation-induced grade 2 liver disease (non-classic RILD).

Survival analyses

Progression free survival

After a median follow up time of 20 months, comparison of PFS between the studied groups showed that there was improvement of the PFS in Arm B compared to Arm A (16 versus 11 months, p value 0.003) (Figure 1). Survival analysis showed that patients who developed CR had the longest PFS (16 months) versus the PR group (8 months), with a p value of 0.002. Hence, CR is noticed to be a prognostic factor for longer PFS. A comparison

Table 3. Post Treatment Outcomes among Studied Groups

		Arm A		Arm B		
		Mean± SD	Range	Mean± SD	Range	p value
AFP after TACE (ng/ml)		38.5± 35	1.9-119	32.3± 31.4	3.9-120	0.556
		N	%	N	%	
Response 1 month after TACE	CR	12	54.50%	10	50%	0.686
	PR	8	36.40%	8	40%	
	SD	2	9.10%	2	10%	
Response 1 month after SBRT	CR	NA	NA	15	75%	NA
	PR	NA	NA	4	20%	
	SD	NA	NA	1	5%	
Child Pugh post TACE or SBRT	A	21	95.50%	18	90%	0.181
	B	1	4.50%	2	10%	
Local or distant metastasis	No	9	41%	10	50%	0.211
	Local	6	27.30%	8	40%	
	Distant	5	22.70%	2	10%	
	Both	2	9%	0	0%	

Table 4. Cox Hazard Regression Model to Assess Prognostic Factors for Relapse among the Included Patients

	Univariate			Multivariate		
	P value	HR	95.0% CI of HR	P value	HR	95.0% CI of HR
Age (years)	0.082	1	0.99-1.08	0.346	1.02	0.97-1.07
SBRT (yes)	<0.001	0.1	0.01-0.26	0.001	0.07	0.01-0.32
Baseline AFP (ng/dL)	0.005	1	1-1.02	0.068	1	1-1.02
Baseline size of lesion (cm)	0.226	0.8	0.55-1.14	0.272	0.81	0.56-1.18
Baseline number of lesions	0.968	1	0.48-1.99			
Number of affected lobes (bilobular)	0.812	0.9	0.44-1.87			
CR after TACE	0.417	0.4	0.04-3.60			

of median local PFS showed a statistically significant difference between the studied groups favoring arm B (16 months) versus arm A (12 months) with a p value of 0.043. A comparison of distant PFS showed a statistically significant difference between groups in favor of arm B (17.5 months) versus arm A (13 months) with a p value of <0.001.

The univariate analysis showed that baseline AFP and receiving SBRT were significantly correlated with PFS; however in the multivariate analysis, we concluded that SBRT is a protective factor from relapse, with a p value of 0.001, and a HR of 0.07 (95% CI 0.01-0.32) after adjustment for age, baseline AFP, and baseline size of the lesion (Table 4). Median overall survival was not reached in both arms.

Discussion

For unresectable HCC tumors that are multifocal or too large for other percutaneous ablative techniques like RFA, TACE is the best current therapy option. TACE is additionally utilized by individuals in need of liver transplants as a bridge; however, it is considered palliative treatment as it has a dismal complete remission rate without satisfactory prolonged PFS [7].

A meta-analysis of 25 studies involving a total number of 2,577 patients with unresectable HCC showed the advantage of combining radiotherapy with TACE (mainly 3-dimensional conformal radiotherapy) with a significant improvement in CR, PR, and 1- to 5-year OS rates in the combination group than in the TACE alone group (P < 0.001). However, most of them indicated that the adverse events, including gastrointestinal ulcers, liver transaminase, and bilirubin elevation were in the combined group [8]. The main goal of addition of SBRT to TACE in our trial was to improve the local control and thereby adding an advantage to the PFS and OS and eventually improving the quality of life in BCLC stage B HCC patients, without adding liver toxicity. As RILD is a major concern when delivering high dose radiotherapy as with SBRT, in our study we attempted to reduce the normal liver tissue dose by taking advantages of VMAT technique. which reduces the dose to the normal tissues through intensity modulation and produces a more conformal dose distribution hence delivering the maximum dose to the target volume with least affection to the organs at risk . The radio-opaque lipdol injected into the tumor by TACE shrinks the tumor and thus reduces the GTV. Additionally, using the breath hold technique helps reduce the PTV margin. CP class A patients were selected to reduce the expected RILB, based on many studies confirming that CP class B patients are more vulnerable to developing RILD than CP class A [9].

A study compared TACE followed by adjuvant SBRT versus salvage SBRT in unresectable BCLC stage B HCC. In comparison, patients who underwent salvage SBRT following incomplete TACE were far less likely to achieve CR (79.6% vs. 43.5%) with planned TACE and SBRT. This supports our idea regarding the benefit of the combined procedure and is comparable to our results [10].

TACE combined with SBRT was studied in another trial. CR was noted in more than 90% of patients compared to TACE alone (40%), with a p value of <0.001. The SBRT group's DFS was noticeably longer (15.2 months versus 4) than the TACE group's. Moreover, no significant RILD was reported in this study. The differences in CR rate between these results and our results (90%versus 75%) can be explained by the difference in sizes of the lesions between the studies, being only single lesion ≤ 3cm in the former study versus 3 lesions with maximum dimension reaching up to 5cm in our study and the radiation dose being 48Gy/4 fractions in the former study due to the smaller lesion size and 40Gy/5 fractions in our trial. Of note, the PFS was almost the same (15 months versus 17 months). Hence, the higher BED and small tumor size improved the results of the local control and added to the PFS [11].

In another study, combined TACE and SBRT for lesions ≤5cm versus TACE alone, which looks a lot similar to our dimensions criteria. This trial included both CP class A and B, alcoholic and viral hepatitis patients. The target lesion was delineated on different respiratory phases to create internal target volume (ITV), followed by a 5mm PTV margin. The PTV received a dosage of 40–60 Gy administered in three to five fractions by cyberknife radiosurgery. Although Delineation was based on ITV which eventually added extra volume to be treated and the dose was up to 60Gy, due to the advanced radiation delivery technique used the overall toxicity was very close to our results although we didn't even have CP class B patients. Within three months of therapy, the CP score worsened by two or more in 9.4% of the SBRT-TACE group and 5.5% of the TACE group, respectively (p = 0.119). In contrast to our trial, where LC was the primary

endpoint and OS and PFS were the secondary endpoints, comparing the OS between the SBRT-TACE and TACE groups was the main endpoint, and the comparison of LC and PFS was the secondary endpoint. The SBRT-TACE group reported a higher LC rate (89.9% at 3 years) than the TACE alone group (44.8% at 3 years). Patients with tumors less than 2 cm had a 100% LC rate at 3 years, patients with tumors 2.1–3 cm had a 93.3% LC rate, and patients with HCC ≤ 4 cm had a 96.3% LC rate at 3 years. In comparison to the TACE groups, the SBRT-TACE group demonstrated superior 1-and 3-year PFS (56.5% and 32.3%, respectively, vs. 42.2% and 21.6%, respectively; p= 0.022).. Our trial scored LC at 75% versus 54.5% and median PFS 16 months versus 11 months. These results can't be compared directly with the results of our trial, as they included both Child score A and B and our trial had Child A only. Despite the appealing results in LC and PFS, the 1-year OS was not different between the SBRT+TACE and TACE groups (99% and 99.7%, respectively; p = 0.206) [12].

Patients who had both TACE and SBRT showed a significant survival benefit following TACE and SBRT compared to TACE alone for large HCC with a median tumor size of 10 cm, according to a propensity score-matched study. Compared to TACE alone, radiological local control was superior in the TACE + SBRT group (98 vs. 56.7%). The TACE + SBRT patients also had improved 1- and 3-year PFS (32.5 vs. 21.4% and 15.1% vs. 5.1%). None of the patients experienced RILD, and TACE + SBRT were well tolerated. In multivariate analysis, TACE + SBRT was an independent positive prognostic factor for OS and PFS, but multiple tumors and AFP >200 ng/ml predicted a worse prognosis. Our trial has also shown that more than 3 lesions contribute to worse PFS and longer follow up is needed to get a proper assessment regarding the OS. In addition, we have noticed that AFP had an influence on the PFS, as seen in the univariate analysis with a non-significant P value in the multivariate analysis (p=0.068) [13].

In 2017, Atsuya Takeda and colleagues studied SBRT and TACE for single-cell HCC that was eligible for radiofrequency ablation and resection. The recommended dosage was 35–40 Gy divided into 5 fractions. The median OS was 56 months, and the 3-year OS rate was 67%. Patients who received 40 Gy/5 fractions had a higher OS rate (67.5% versus 60%, respectively) than those who received 35 Gy/5 fractions, according to subgroup analysis. In our investigation, the median OS was not reached. The LC rate over three years was 96.3%. Six percent of patients had grade 3 laboratory abnormalities, and 8% of them had CP scores that worsened by two points. This study shows that SBRT is a valid substitute for individuals who are not candidates for liver transplantation, RFA, or surgery [14].

The optimal SBRT dosage for HCC was investigated in a retrospective study, and the dosage was classified into BED ≥ 100 Gy and BED < 100 Gy. OS, PFS, and LC were evaluated in univariable and multivariable analyses. Multivariable Cox regression analysis showed that BCLC stage was a predictor of LC, PFS, and OS, and higher radiotherapy doses was a predictor of better PFS and OS. BED100 ≥ 100 Gy was recommended as the first-line ablative dose and BED <100 Gy can be used as a second-line radical dose otherwise as palliative irradiation. Our patients were treated with 40Gy/5 fractions, which is equivalent to BED 88Gy, however, higher doses were not selected to avoid RILD and other GIT symptoms, especially with the lack of tumor tracking methods based on fiducial markers insertion. Using advanced radiation therapy machines guided by IGRT with verification techniques of high accuracy is needed to be able to reach a higher BED with a minimal toxicity profile, hence increasing the therapeutic ratio.

Adding SBRT to TACE in cases of inoperable HCC, not candidate for ablation or liver transplantation is safe and feasible, and has improved the outcome in terms of LC and PFS. Liver toxicity was very modest, making the procedure well tolerated. Longer follow up and larger sample size is needed to achieve more clear results regarding OS. We faced some challenges when conducting our study that included logistic, financial and technical difficulties taking into consideration the patient's daily transportation, overall treatment time, machine overload and close follow up of the patients fearing adverse events.

Degree of liver cirrhosis needs to be assessed to be able to stratify the patients and see the relation between the cirrhosis degree and the tolerability and where cirrhosis has an impact on the prognosis.

Author Contribution Statement

All authors contributed equally in this study.

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Approval

The study was approved by the ethics research committee of the faculty of medicine, Cairo University. (Ref: MD-128-2021).

Conflict of Interest

The authors declare no conflict of interest.

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