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Low applicability of the ‘‘six-and-twelve score” in hepatocellular carcinoma treated with drug-eluting beads transarterial chemoembolization

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Abbreviations:

TACE: transarterial chemoembolization

HCC: hepatocellular carcinoma

DEB-TACE: drug eluting beads-transarterial chemoembolization

BCLC: Barcelona Clinic Liver Cancer

OS: overall survival

AIC: Akaike's information criterion

LRT: likelihood ratio test

EASL: European Association for the Study of the Liver

ECOG-PS: Eastern Cooperative Oncology Group -Performance Status

CPS: Child-Pugh score

CBCT: Cone Beam Computed Tomography

mRECIST: modified Response Evaluation Criteria In Solid Tumors

IQR: interquartile range

CI: confidence interval

AFP: Alpha-fetoprotein

AP: alkaline phosphatase

AUROC: Area Under the Receiver Operating Characteristics

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Abstract:

Objective: The effectiveness of transarterial chemoembolization (TACE) in hepatocellular carcinoma (HCC) depends on the selection of suitable patients. The ‘‘Six-and-twelve score” distinguishes three groups of ideal patients with different overall survival based on the sum of number and size of tumors. This may impact clinical practice and trials design. The aim of the study is to assess the reproducibility and the prognostic value of the model in western patients treated with Drug-Eluting Beads (DEB)-TACE. **Methods:** observational, retrospective, unicentric study developed in consecutive compensated patients treated with DEB-TACE from October/2008 to October/2017. Exclusion criteria were Child-Pugh ≥ 8 and DEB-TACE used as a bridge to liver transplantation. **Results:** 225 HCC consecutive patients were included, BCLC-0/A n=131 (single nodules > 5, n=29), BCLC-B n=94. The median overall survival (OS) was 27 months (95% CI 23.8-30.2). OS was different between BCLC-0/A vs B: 30 vs 24 months (p= 0.03), Child-Pugh A5 vs A6-B7: 30 vs 27 months (p= 0.003). ‘‘Six-and-twelve score” groups discriminated OS: group 1, n=123, 32 months (95% CI 27.5-63.5); group 2, n=101, 24 months (95% CI 19.6-28.4) and group 3, n=1, 27 months (p=0.024). When comparing the three scores, the ‘‘Six-and-twelve score” showed the best discrimination power: C-index 0.603, Akaike’s information criterion (AIC) 1.642, likelihood ratio test (LRT) 16.21. **Conclusion:** The ‘‘Six-and-twelve score” is a prognostic tool for patients with HCC treated with DEB-TACE. However, few patients were included in the third group (score >12) and no differences were observed with BCLC, therefore its applicability is limited.

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Introduction:

Transarterial chemoembolization (TACE) is the first-line treatment for asymptomatic patients with multinodular hepatocellular carcinoma beyond the Milan criteria, without portal invasion or extrahepatic disease and compensated liver function. It is also performed in earlier staged HCC if resection, ablation or liver transplantation are not feasible (1). Considering the heterogeneity of TACE candidates, patient selection is a key step to obtain success with therapy. During the last number of years, several algorithms have been built up to predict HCC prognosis in an attempt to optimize chemoembolization treatments, both to improve the patient selection for the first TACE (2-10) and to recommend subsequent TACE (11-14). In 2019, Wang et al. developed the ‘‘Six-and-twelve score” in an Asian cohort of ideal TACE candidates with liver damage mainly due to hepatitis B and treated with conventional TACE. The score was carried out by adding the number of nodules and the main nodule size (15). This model stratified 3 groups with significant differences in overall survival: group 1 (score ≤6) 49.1 months, group 2 (score >6 but ≤12) 32 months, group 3 (score >12) 15.8 months. Afterwards, Boulière et al. validated the score in a multicentric French cohort of patients with liver cirrhosis mainly due to alcohol, and treated with conventional TACE as well. However, prognostic performance of the score was lower in this cohort, which was attributable to alcohol abuse (16).

Therefore, the aim of this study is to perform a second external validation of the “Six-and-twelve score” focused in a western unicentric cohort of patients treated with DEB-TACE in real clinical practice.

Materials and Methods:

HCC was diagnosed according to the European Association for the Study of the Liver (EASL) guidelines (17). All patients with HCC diagnosis from October 2008 to October 2017 were evaluated in a western tertiary academic university hospital, prospectively registered and selected for DEB-TACE. Clinical, biochemical and radiological examinations were performed at baseline and prior to every DEB-TACE procedure.

The inclusion criteria were: 1) very early and early-stage HCC not eligible for resection or ablation and intermediate stage HCC naïve to TACE, according to Barcelona Clinic Liver Cancer classification (BCLC) (1); 2) asymptomatic status, ECOG performance status 0; 3) approval for DEB-TACE after evaluation by the multidisciplinary tumour board.

Portal thrombosis; impaired liver function (Child-Pugh score, CPS ≥8); patients included in clinical trials; patients treated while awaiting liver transplantation; patients with recurrence after liver transplantation; decompensated cirrhosis; performance status > 0; extrahepatic disease and contraindication or impossibility for catheterization or chemoembolization were considered as exclusion criteria. Those with tumour size unspecified or pre-treatment CPS not available were also discarded.

Patients with previous hepatic decompensation were not excluded if compensated at the time of DEB-TACE, and neither those who received resection or ablation prior to DEB-TACE.

DEB-TACE procedure has been described elsewhere (18). The day before the procedure, drug-eluting beads (DC-Bead™ Boston Scientific) were loaded with doxorubicin following the manufacturer's instructions. A supraselective approach was always intended by employing 300-500 microns (µm) particles until March 2013, when they were replaced by 100-300-µm beads to penetrate further into the tumour (19). From February 2015, Cone-Beam-CT (CBCT) software (syngo DynaCT, Siemens™) was routinely applied.

Follow-up: Clinical, analytical and radiological follow-up was appointed 6 weeks after each DEB-TACE procedure. Response to treatment was assessed by contrast-enhanced CT according to the modified Response Evaluation Criteria In Solid Tumors (mRECIST) criteria (20). Subsequent DEB-TACE was discussed in the multidisciplinary tumour board and performed on-demand, considering response to treatment (21).

Statistical analysis:

Data were analyzed using the statistical package SPSS version 23 (SPSS Inc., Chicago, IL) and R (http://www.R-project.org/ libraries rms, timeROC, and survival). Continuous variables were summarized using median values and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Continuous quantitative variables were categorized according to the median value for the analysis. The Mann–Whitney and the χ2-test tests were used to compare continuous and categorical variables respectively. A two-tailed *P* value <0.05 was considered to be statistically significant. Overall survival (OS) was calculated from first DEB-TACE to end of follow-up, which was censored at death, loss to follow-up or last visit (24th October 2019). Kaplan–Meier statistics followed by stepwise backward Cox regression were used for univariate and multivariate analyses of survival. The accuracy of the "Six-and-twelve score", BCLC staging system and Child-Pugh score was assessed in terms of homogeneity, discriminatory ability and monotonicity. Discriminatory ability was estimated using Harrel´s c-index.

Ethical Approval:

No specific individual consent was obtained regarding the retrospective nature of the publication. Institutional Review Board approval was obtained. The protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee (Approval No. 120/19).

Results: Baseline characteristics (n=225) are summarized in **Table 1**. A total of 187 patients (83%) were male with a median age of 70 years (IQR 65-76.5). The main etiology of liver disease was alcohol (n=107), followed by hepatitis C (n=70). Liver function was well-preserved in 208 patients (165 with CP A-5 and 43 with CP A-6), while 17 patients were CP B-7. Twelve (5%) patients were BCLC-0, 119 (53%) BCLC-A, 29 of which had a single nodule larger than 5cm, and 94 (42%) BCLC-B. DEB-TACE was the first treatment for HCC in 166 (74%) patients. Seventy-seven patients (34%) had liver decompensation previous to TACE with a median of 25.5 months between the last episode of decompensation and TACE treatment.

The median size of the main nodule was 3.5cm (IQR 2.5-4.8) and the median number of nodules was 2 (IQR 1-3). The median value of the "Six-and-twelve score" variable was 6 (IQR 4.5-7.4).

By stratifying according to the "Six-and-twelve score" groups, 123 patients were included in group 1, 101 in group 2 and only 1 in group 3.

Follow-up and overall survival:

After a median follow-up of 25 months (IQR 14-38.5), 187 (83%) patients had deceased while 38 (17%) remained alive. Median OS was 27 months (95% CI 24.04-29.9) (**Figure 1a**). No differences in OS were observed between patients with and without previous decompensation [25 months (95% CI 20.7-29.3) vs 27 months (95% CI 23.5-30.5), p= 0.58, respectively] **(Figure 1b)**.

Alpha-fetoprotein (AFP), alkaline phosphatase (AP), bilirubin and prothrombin time were statistically significant in the univariate analysis. In the multivariate analysis the variables with significant association with OS were AFP plus AP (**Table 2**).

After the first DEB-TACE, objective response (the addition of complete and partial response) was achieved in 161 patients (72%). Thirty-five patients (15%) presented progressive disease. The median number of DEB-TACE sessions was 2 (IQR 1-3). Sixty-nine patients (30.7%) switched to sorafenib during follow-up.

One hundred thirty-seven patients (61%) did not experience any post-TACE event. Hepatic decompensation was observed in 33 patients (15%).

Applicability of the "Six-and-twelve score": BCLC, Child-Pugh and the "Six-and-twelve score" were able to discriminate groups of patients with significantly different OS (BCLC-0/A vs B: 30 months vs 24 months, p= 0.03; CP A-5 vs A6-B7: 29 months vs 20 months, p= 0.005; "Six-and-twelve score" group 1, 31 months (95% CI 25.9- 6.1) vs group 2, 24 months (95% CI 19.6-28.4) vs group 3, 27 months (p=0.048)). **Figure 2** depicts the Kaplan-Meier curve of each score. The Area Under Receiver Operating Characteristic curve (AUROC) and C-index of the three scores are shown in **Table 3.**

Time-dependent AUROC values and C-index of the "Six-and-twelve score" were not significantly different from those obtained with BCLC and Child-Pugh within our

cohort.

Alcohol-related cirrhosis was significantly associated to male gender, younger age of HCC diagnosis and a higher rate of prior decompensation (**Table 4**). In patients with alcohol cirrhosis and HCC treated with DEB-TACE the best prognostic score to assess OS was Child-Pugh (p=0.04) in comparison with the "Six-and-twelve score" (p=0.39) and BCLC (p=0.14).

Discussion: Several scores have been set up to elucidate the best way to select patients for TACE treatment. This study aims to show the applicability of the new model "six-and-twelve score" in a real practice scenario of western patients treated with DEB-TACE.

TACE treatment is theoretically precluded in patients with vascular invasion, hepatic decompensation, CP>7 and relevant comorbidity (22). The "Six-and-twelve score" and the external French validation were applied to naïve patients without prior history of liver decompensation or peritoneal bleeding. By contrast, we have decided to include patients with prior thermal ablation or hepatic resection as well as patients with previous liver decompensation that were compensated at the moment of the DEB-TACE to resemble a clinical practice context (23).

Unlike in the article by Wang et al., although the "Six-and twelve score" discriminates groups with different OS in our cohort, no differences were observed with other standardized scores like CPS or BCLC. However, our findings are consistent with what Bourlière el al. described. As that the French group pointed out, some remarkable differences were observed regarding to the original study. First of all, just one patient was included in the third group of the score. As it was previously mentioned, some candidates to TACE migrate to systemic therapy because of tumour burden (5). Secondly, just like in the French validation cohort, OS is lower than in the Chinese one. Alcohol was the main cause of liver disease in our region (24). Poorer outcomes have been reported in alcohol-related liver diseases in comparison with other etiologies (25-27). Although alcohol etiology did not reach independent prognostic value, lower median age of diagnosis, higher rate of previous clinical decompensation and lower survival were observed in these patients. This may suggest not only a more advanced

liver damage but also the outstanding role of the psychosocial factors associated with chronic alcohol consumption (28, 29).

On the other hand, it could be hypothesized that patients in groups 2 or/and 3 would be better switched to TARE or systemic treatment. In this line of reasoning there are some recent publications with a survival of 19 months in Bolondi's BCLC-B2 patients treated with TARE (30).

This study has several weaknesses. Firstly, this is a unicentric retrospective study with uncontrolled biases and the sample size is not comparable to the Chinese cohort. Secondly, we have included non-naïve HCC patients and some of them had prior liver decompensation, so the inclusion criteria were not exactly the same as those of the original Chinese article. However, this study is the first one that validates the "Six-and-twelve score" in a DEB-TACE cohort.

In conclusion, the "Six-and-Twelve score" discriminates groups with different OS. However, a scarce number of patients was included in the third group (score >12) and no differences were observed in its discriminatory ability compared with BCLC, therefore the applicability is limited.

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Table 1. Baseline characteristics of the patients (n=225).

Table 1

Age (yr), median (IQR)	70 (65-76.5)
Gender (Male/Female), n (%)	187 (83) /38 (17)
Alcohol/HCV/other etiologies, n (%)	107 (48)/ 70 (31)/ 48 (21)
Esophageal varices (no/yes/not available), n (%)	74 (33)/136 (60)/15 (7)
Child-Pugh (A5/ A6/ B7), n (%)	165 (73)/ 43 (19)/ 17 (8)
BCLC-B (0/A/B), n	12 (5)/119(53)/94 (42)
Six-and-Twelve (1/2/3), n (%)	123 (54.9)/101 (44.9)/1 (0.1)
Bilirubin (mg/dL), median (IQR)	1 (1-1.3)
Albumin, (g/L), median (IQR)	41 (37-43)
AFP (ng/mL), median (IQR)	11.2 (4.73-60.55)
Cr (mg/dL), median (IQR)	0.85 (0.72-1)
Sodium (mEq/L), median (IQR)	141 (139-142)
AST (IU/L), median (IQR)	44.5 (29-75.25)
ALT (IU/L), median (IQR)	35 (24-78)
GGT (IU/L), median (IQR)	113 (67-187)
AP (IU/L), median (IQR)	105 (85-137.75)
PT (%), median (IQR)	84 (75-93)
Platelets (x 10^9/L), median (IQR)	118 (81-163)
Hemoglobin (g/dL), median (IQR)	13.65 (12.5-14.9)
Main nodule diameter (mm), median (IQR)	35 (25-48)
Previous treatment (none /ablation /resection), n	166 / 50 / 9
Prior decompensation (no / yes)	148 /77

Yr: year; IQR: interquartile range; HCV: hepatitis C virus; BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; Cr: serum creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl-transpeptidase; AP: alkaline phosphatase; PT: prothrombin time.

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Table 2. Predictors of overall survival based on multivariate Cox regression.

Table 2.

			Univariate analysis			Multivariate analysis		
Variable	Categories	n =225	Overall survival (months)		p-value	HR	HR 95% CI	p-value
			median	median 95% CI				
Esophageal varices	No varices	74	31	24.2 - 37.8	0.126			
	Varices	136	25	20.9 - 29.01				
Gender	Men	187	32	22.9 - 41	0.143			
	Women	38	26	23.5 - 28.				
Age	<70	115	27	23.3 – 30.7	0.279			
	≥ 70	110	27	22.6 – 31.4				
Etiology	Alcohol	126	25	22.3-27.7	0.224			
	Other	99	29	25.3-32.3				
Tumor size	< 35 mm	118	30	26.8 - 33.2	0.150			
	≥ 35 mm	107	24	19.9 - 28.1				
Number of nodules	≤3	189	27	23.3 - 30.6	0.313			
	>3	39	26	18.6 - 33.				
AFP*	<median	111	29	25.9- 32.1	**0.015**	0.72	0.54-0.96	**0.028**
	≥median	109	24	19.9 - 28.				
Bilirubin*	<median	141	27	23.5 - 30.43	**0.014**			
	≥median	84	25	20.5 - 29.4				
Albumin*	<median	133	25	20.8- 29.1	0.381			
	≥median	92	27	23.5 - 30.5				
AST*	<median	107	27	23.9 - 30.1	0.585			
	≥median	107	27	22.9 - 31.02				
ALT*	<median	113	27	23.9 - 30.1	0.555			
	≥median	113	28	24.9 - 31.1				

GGT*	<median	108	27	21.1 - 32.9	0.247			
	≥median	107	26	22.8 - 29.2				
AP*	<median	152	30	25.3 - 34.4	**0.011**	0.72	0.53-0.98	**0.037**
	≥median	72	24	20.9 - 27.02				
Creatinine*	<median	118	27	23.7 -30.3	0.433			
	≥median	106	27	22.3 - 31.7				
Na*	<median	146	27	23.3 – 30.6	0.780			
	≥median	60	25	21.4 – 28.6				
Prothrombine time*	<median	113	24	20.3 - 27.7	**0.039**			
	≥median	112	30	26.3 – 33.7				
Hemoglobin*	<median	112	26	21.9– 30.1	0.266			
	≥median	112	27	23.9 – 30.1				
Platelets*	≤ median	113	26	22.5– 29.5	0.411			
	> median	110	27	21.8 – 32.2				
Previous decompensation	NO	148	27	23.5 - 30.5	0.068			
	YES	77	25	20.7 - 29.3				
BCLC	BCLC-0/A	131	30	25.7-34.3	**0.03**			
	BCLC-B	94	24	20.2-27.8				
Six-to-Twelve	Group 1	123	31	25.9 - 36.1	**0.048**			
	Group 2	101	24	19.6 - 28.4				
	Group 3	1	27					
Child-Pugh	A5	165	29	25.9 - 32.04	**0.005**			
	Other	60	20	13.9 - 26.04				

CI: confidence interval; HR: hazard ratio; TACE: transarterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; AP: alkaline phosphatase.

*Median values: AFP 11.2 ng/mL; Bilirubin 1,00 mg/dL; Albumin 41 g/L; AST 44.5 UI/L; ALT 35 IU/L; GGT 113 IU/L ; AP 105 IU/L; Hemoglobin 13.65 g/dL. Platelets $118x10^9$/L.

Table 3. AUROC and C-index of the three prognostic models: “Six-and-twelve score”, BCLC-staging system and Child-Pugh score.

	AUROC									c-index			AIC	LR	
	1 year			2 year			3 year								
	AUROC	95% CI	p-value	AUROC	95% CI	p-value	AUROC	95% CI	p-value	value	95% CI	p-value		value	p-value
Six-to-twelve score	0,574	0,491-0,657	Ref*	0,566	0,497-0,634	Ref*	0,580	0,507-0,653	Ref*	0,603	0,559-0,647	0,000	1.642,49	16,21	0,01
BCLC system	0,525	0,441-0,608	0,5051	0,556	0,487-0,624	0,980	0,563	0,490-0,635	0,926	0,587	0,541-0,633	0,000	1.642,94	15,8	0,01
Child-Pug	0,577	0,497-0,967	0,999	0,573	0,513-0,647	0,996	0,588	0,529-0,647	0,996	0,594	0,548-0,640	0,000	1.645,43	18,27	0,02

h grad e															

AUROC: Area Under the Receiver Operating Characteristics

C-index: concordance- index

AIC: Akaike information criterion

LR: *Likelihood ratio*

*Ref: ref stands for the reference for the comparison.

Table 4. Baseline characteristics according to the etiology of cirrhosis (alcohol vs others).

Variables	**Alcohol (n=126)**	**Non alcohol (n=99)**	**p-value**
Age, median (IQR)	69 (64-67)	74 (66-78)	**0.001**
Gender (men / women), n	122 / 4	65 / 34	**< 0.001**
Diameter (mm), median (IQR)	32 (25-44.3)	36 (25-50)	0.09
Number of nodules, median (IQR)	2 (1-3)	2 (1-3)	n.s
Prior treatment (no / yes), n	91 / 35	70 /29	0.8
Child-Pugh score (A5 / A6 / B7), n	96 / 19 / 11	69 / 24 / 6	0.19
Past decompensation (no / yes), n	67 /59	81 / 18	**<0.001**
Months from decompensation to DEB-TACE, median (IQR)	33 (8-98)	20 (4-34)	0.16
BCLC stage (0 / A / B), n	4 / 66 / 56	8/ 53/ 38	0.21
“Six and Twelve” score (1/2/3), n	71 / 55 / -	52 /46 / 1	0.47
OS (months), median (IQR)	25 (22.3-27.7)	29 (25.3-32.7)	0.22

IQR: interquartile range; OS: overall survival; n: number; n.s: non-significant.

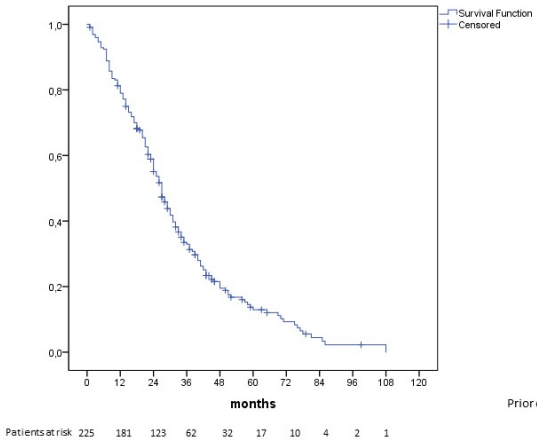

Figure 1a

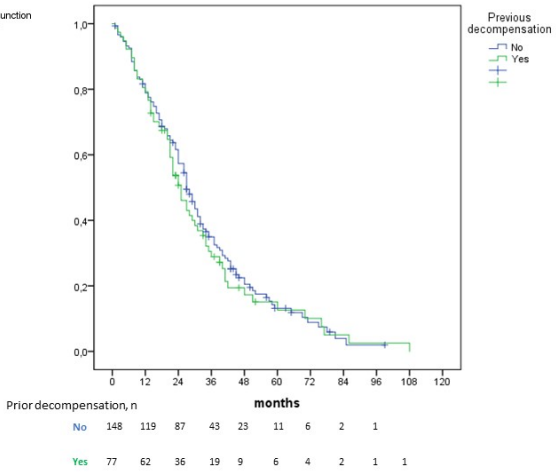

Figure 1b

Fig. 1. Kaplan-Meier plot showing the global OS (median OS 27 months (95% CI 24.04-29.9) (**fig 1a**). Kaplan-Meier plot of OS according to prior decompensation of liver disease: no decompensation median OS 27 months (95% CI 23.5-30.5) vs prior decompensation median OS 25 months (95% CI 20.7-29.3), p= 0.59 (**fig 1b**).

Figure 2

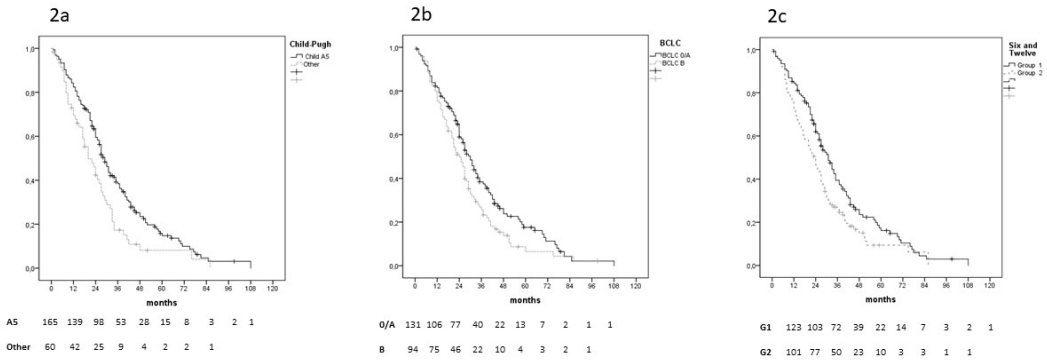

Fig. 2. Kaplan- Meier plot of overall survival in Child-Pugh A5 vs A6-B7 (**fig 2a**), BCLC-stage 0-A vs B (**fig 2b**) and Six-and-twelve score group 1 vs 2. *Group 3 was excluded*

from the figure because there is only one patient included **(fig 2c**).