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Post Embolization Syndrome in Doxorubicin Eluting Chemoembolization with DC Bead

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ABBREVIATIONS: Post Embolization Syndrome (PES); Hepatocellular Carcinoma (HCC).

ABSTRACT

Background/Aims: The investigation of Post Embolization Syndrome (PES) in patients with Hepatocellular Carcinoma (HCC) after treatment with doxorubicin loaded DC Bead (DEB-DOX). **Methodology:** The study included 237 patients treated with sequential DEB-TACE performed at set time intervals every two months until 3 sessions/6 month f-u. Patients were ECOG 0-1, Child-Stage-A (n=116, 48.9%) and B (n=121, 51%). Embolizations were as selective as possible with DC Bead of 100-300μm in diameter followed by 300-500μm loaded with doxorubicin at 37.5mg/mL of hydrated bead (max:150mg). **Results:** PES regardless of severity was observed in up to 86.5%. However grade 2 PES ranged between 25% and 42.19% across treatments. Temperatures above 38°C were seen in 22.7% to 38.3% across treatments. No statistically significant increase of PES was seen in beads of 100-300μm in diameter; incidence of fever and pain presented correlation with the extent of embolization (p=0.0001-0.006 across treatments). Baseline tumor diameter was associated with incidence of fever (p=0.0001-0.001). Duration of fever correlated with the extent of embolization (p=0.008). PES was not associated with elevation of liver enzymes and was correlated with degree of necrosis (p<0.001). **Conclusions:** PES after DEB-DOX represents tumor response to treatment and does not represent collateral healthy liver damage.

INTRODUCTION

Since 2002 the use of trans-arterial chemoembolization (TACE) techniques for hepatocellular carcinoma (HCC) in patients with BCLC B disease has increased mainly as a result of a) the proof of survival benefit of conventional chemoembolization (c-TACE) (1-3) and the proven advantage of doxorubicin eluting beads TACE (DEB-TACE) over conventional TACE (c-TACE) (4).

The increased use of the newly introduced DEB-TACE necessitates a re-appraisal of complications. Regarding Doxorubicin eluting DC Bead embolization (DEB-DOX) for HCC there are two papers focusing exclusively in complications, the first originating from a randomized study comparing DEB-DOX embolization with conventional chemoembolization (c-TACE) (5) and the second being a large case series (6). In these studies post embolization syndrome (PES) has been recorded with various frequencies (7-11). The description of this syndrome in these papers is not sufficiently described and no attempt of quantification of severity has been published. In the National Cancer Criteria for adverse events there is no precise term to assist in accurate description and quantification of this condition (12,13). In addition, only a few papers present correlation of the incidence and severity of PES with embolization parameters or with lesion features and these studies refer only to c-TACE (14-18). This is the first study that focuses on PES as a complication of DEB-DOX; incidence, severity and correlations with embolization technique, liver function and baseline tumor characteristics are presented.

METHODOLOGY

Study population

Data have been obtained prospectively from 237 patients treated with sequential DEB-TACE performed at set time intervals every two months until 3 sessions/6 month f-u. Patients had BCLC B stage of HCC, were ECOG 0-1, Child-Stage A (n=116, 48.9%) and B (n=121, 51%).

Procedure

After feeding arteries were selectively/super-selectively catheterised with the use of a 2.4 or 2.7Fr micro-catheter (Progreat, Terumo) injection of the DC Bead loaded with doxorubicin followed, until the complete intended dose was administered or until intratumoral vascularity was obliterated. The diameter of the beads was based on the size of the lesion, the feeder diameter and vascularity. Two different sizes of DC Bead were used, 100-300μm and/or 300-500μm. Doxorubicin was loaded at the level of 37.5mg/mL of hydrated beads at a total dose of 150mg doxorubicin per patient. When flow stasis was not achieved additional embolization with Beadblock particles followed (Biocompatibles, Terumo).

The size of the beads used were classified as size 1 (small beads of 100-300μm only), size 2 (100-300μm followed by 300-500μm) and size 3 (those in which additional Bead block of similar diameters was used (Biocompatibles, Terumo). In addition, quantity of the beads in vials was recorded along with the type of embolization including super-selective (SS), selective (S) and more extensive embolization (>S).

Hydration was administered before and after the embolization. All patients received antibiotic prophylaxis (Cefuroxime sodium/Zinacef 750mg IVq/8h, 500mg Metronidazole), 500mg Solucortef or 10mg Dexamethasone, 100mg Ranitidine IV (Zantac) and antiemetic drug (8-16mg Ondansetron/Zofron IV). Pain was controlled individually with non steroidal anti-inflammatory drugs or opioids according to the interventionalist's preference (Lornoxicam 4-16mg or Tramadol 50-200mg/24h by MP and Tramadol 50-200mg or Pethidine 50-200mg/24h by KM and HM).

Imaging follow-up

Patients were followed-up at 1, 3 and 5-6 months, *i.e.* one month after each procedure with computed tomography (CT) or magnetic resonance imaging (MRI) with Contrast Enhanced Ultrasound (CEUS) as an additional imaging technique. Ultrasound without contrast was done before patient discharge in those patients with severe pain. Imaging response was classified according to the EASL criteria (19).

Safety

Safety was monitored by follow-up of liver enzymes before discharge and synchronously with the scheduled imaging follow up visits. Liver function tests included bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and albumin levels. Amylase levels were obtained in cases of prolonged abdominal pain (≥3 days). The latest National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) (12,13) were used to grade severity of PES. Grade 1 complications are mild, require no intervention. Grade 2 events require bedside medical management requiring medication. Grade 3 complications are severe that require additional intervention, Grade 4 complications are those that are life- threatening and/or result in chronic disability and a Grade 5 complication is a death related to the adverse event. PES grade 1 (mild) was when no systemic administration of treatment was required and as PES grade 2 this required administration of analgetics on a daily basis (severe).

Data analysis

Comparisons between non-parametric variables were performed with the Mann-Whitney U-test or Pearson χ^2 test as appropriate. Pair wise comparisons through multivariate analysis and cross-tabulations were performed in order to identify differences between the mean values of bilirubin, AST,

ALT (in above mentioned time points) and PES in relation to the levels of the independent variable (DC Bead and Beadblock size and quantity, Embolization Type). SPSS software version 11.5.0 was used and the statistical level of significance was set on 0.05.

RESULTS

Table 1 shows the clinical and laboratory profile of the patients included in this study. PES regardless of severity was observed in up to 86.5%. However grade 2 PES requiring medication ranged between 25% and 42.19% across treatments. Mean duration of pain was 3.5±2.7 days (0-9). Mean duration of fever was 2.9±2.1 days (0-5). Mean morning fever was 37.8±1.9°C while levels above 38°C were seen in 22.7% to 38.3% across treatments. In **Table 2** incidence of fever and pain is correlated with the size of the beads and a statistical significance is revealed only between pain and the combined bead diameters ($p<0.0001$) while no correlation was present for the small diameter of beads of 100-300μm ($p=0.09$-0.3). **Table 3** shows the correlation coefficients between extent of embolization and incidence of fever and pain that result in statistical significance both for pain ($p=0.001$-0.015) and fever ($p=0.006$-0.0001) across treatments.

Baseline tumor diameter was associated with incidence of fever ($p<0.001$ to $p<0.0001$) and more specifically the duration of fever correlated with the diameter of the tumor ($p=0.02$) as seen in **Figure 1A**. Pain duration did not correlate with baseline tumor diameter (**Figure 1B**). Patients with objective response (CR+PR) presented higher rates of PES compared to those with SD ($p<0.001$).

The duration of fever was more frequently seen in combined bead diameters of 100-300 followed by 300-500μm ($p=0.009$) while the small bead diameter (100-300μm) was not associated with longer duration of fever (**Figure 2A**). In addition, fever duration correlated with the extent of embolization ($p=0.008$) (**Figure 2B**). Duration of pain did not correlate neither with bead size, nor with extent of embolization ($p=0.20$ and 0.54 respectively). During PES there was no statistical significant change in liver enzymes and bilirubin which did not present clinically meaningful elevations (**Figure 3**).

Figure 4A demonstrates the correlation of rates of grade 1 and grade 2 PES stratified per size of the beads and shows no statistically significant correlation for beads of 100-300μm while for combined bead diameter correlation was revealed ($p=0.019$). **Figure 4B** shows that both grade 1 and grade 2 PES are associated with the extent of embolization ($p=0.001$). Finally PES correlated positively with the quantity of beads used ($p=0.012$). In all cases PES was managed with symptomatic treatment.

DISCUSSION

Post-embolization syndrome (PES) is characterised by the combination of right abdominal pain, fever fatigue, nausea and vomit of any severity (14-22). Some investigators limit PES to body temperature above 38°C and pain that requires analgetics for more than a week (14,15). In our series we classify

PES as mild (grade1) when no systemic medication is needed and PES as severe (grade 2) when systematic administration of analgesics is needed. Huo *et al.* include in the definition of PES a 5-fold increase of transaminases from baseline values and classify mild PES as duration of less than 3 days and severe PES as this of more than 3 days (23). Paye *et al.* and Wigmore *et al.* in their definition of PES include fever and cytolysis (further defined as increase of AST levels >100 IU/L and >2-fold pre TACE values (17,18). However the increased liver enzymes are not consistently reported in PES and this elevation was not seen in our patient series.

The incidence rate of PES overall in our series was within the range observed in other clinical series with DEB-DOX embolization; PES was observed in 77.1% in Poon's series and the symptoms were characterized as mild (8). In the study of Varela *et al.* PES was reported in only 10 of the 27 patients (37%), who responded well to acetaminophen or tramadol and did not require prolonged hospitalization (7). In their study they describe mild fever (<38.0°C), nausea and vomiting in 22 and 15% respectively (7). After the second embolization 18% of their patients presented PES with 32% mild pain and 14% nausea and vomiting and no symptoms remained after one week. Malagari *et al.* report PES in all of their earlier reports without further classification of severity (9,10). Vogl *et al.* report very low rates of PES at both c-TACE and DC Bead group in the randomized study comparing these two treatments reaching 25.9% and 24.7% respectively (5). In all these studies the dose of doxorubicin was similar.

One of the difficulties in comparing results among studies is that PES comprises of one manifestation that can be quantified (fever) and pain and nausea that are difficult to quantify. An alternative more objective index though is the duration of these symptoms and this is the reason in this series we evaluated frequency and duration as well. Notably, in our study grade 2 PES requiring systematic analgetics was 25% to 42.19% across treatments. These incidences show similar or lower rates of PES compared to c-TACE (14-16,20,22). However, not all studies clearly define the threshold of fever and pain to call PES, a fact that compromises comparisons. Mean duration of pain in our study was 3.5±2.7 days (0-9) while duration of fever was 2.9±2.1 days (0-5), rates that are comparable with c-TACE (1,24-28). However, the rate of temperature above 38°C was 22.7% to 38.3% across treatments, that is lower to c-TACE (15,20,22,24-30).

Overall, PES is reported more frequently in c-TACE compared to DEB-DOX at rates ranging from 15.1% to 100% (15,24,25,27-30). Chan *et al.* in 59 patients with 197 sessions post TACE report fever in 74%; the mean duration was 3.4 days±2.7 (0-30) and mean highest temperature of 37.62±2.8°C (24). In the same study pain was seen in 45.2%, and nausea in 58.9%. Li *et al.* report fever in 73% of their patients; none of these patients developed infection (25). Lo *et al.* with 40 patients and 192 sessions report PES related fever in 32.8%, pain in 26% and vomiting in 16.7% (1). In the French study, PES was seen in 86% of sessions and lasted 2.5±2.1 days (range 1-10) (26). In addition they

found that body temperature above 38°C developed in 49%, pain in 45.2% and vomiting in 57%. Chen *et al.* with 289 patients post c-TACE report PES related fever in 100%, chills 80% and pain in 80% that lasted for more than a week (28). Pelletier *et al.* with 37/73 of their patients post TACE with 103 sessions report fever in 74%, pain in 43% (27). Bronowicky *et al.* in 127 patients post TACE report fever in 100% and pain in 53% (29). Stefanini *et al.* report fever in 46.2% and pain in 36.6% overall (30). Chung *et al.* (14) in 351 patients post TACE (340 with HCC) report severe PES 15.1%. Huo *et al.* in 140 patients post TACE report PES in 94%, fever in 71% and nausea and vomiting in 93% and classify it as mild in 61% and severe in 33% (23). Takayasu *et al.* (31) reported high body temperature (>38°C) in 72.2% and abdominal pain with nausea and vomiting in 16.7%, which are definitely lower than the rates observed in our study.

The fact that duration of fever showed significant relation with the baseline diameter of the tumor ($p<0.001$ to $p<0.0001$) indicates that fever is related with the induced necrosis of the target tumor. In addition, the low degree of liver enzymes elevation shows that non target embolization was not the cause of PES. Duration of pain did not correlate with baseline tumor diameter, a fact that may indicate that pain mechanism is not clearly understood. The fact that pain duration correlated with extent of embolization (in the absence of elevated liver enzymes) may simply reflect that larger tumors require embolization of more than one segment. In addition, it was proven in our series that patients with more extensive necrosis as classified by the EASL criteria presented higher incidence of PES compared to the poor responders with stable disease.

Other studies also attribute PES to the extent of tumor necrosis and consider it a positive prognostic sign of increased local response to treatment (16,26,32-34). Similarly to our study Chan *et al.* found that the duration of fever correlated positively with initial tumor size, the total dose of cisplatin but also found a correlation with pre-treatment AST (24). Li *et al.* also found that PES frequency correlated with tumor size and quantity of lipiodol and chemotherapeutic (25). Finally in c-TACE case series PES has also been attributed to pulmonary ethiodol embolization (14).

This explanation of PES has been questioned by Paye *et al.* and Wigmore *et al.* who suggest that PES is rather an adverse event than tumor response and is attributed to damage of the adjacent liver (17,18). In their paper Paye *et al.* with 29 patients with HCC who had tumor resection post c-TACE showed that cytolysis developed in 55.17% of their patients and correlated positively with PES while on the contrary PES was not seen in the absence of cytolysis irrespective of tumor necrosis. However, their study was retrospective and c-TACE was performed with lobar catheterization without selective approach (17). Wigmore *et al.* (18) also correlate PES with cytolysis; in 145 patients with HCC and liver metastasis report PES in 41% and increased transaminases (cytolysis) in 93% the most prevalent of which was increase of AST (+158) despite the fact that they performed selective embolization in 89% of the sessions. The absence of cytolysis in our series could be attributed to the gradual long term

elution of doxorubicin from the DC Bead and the selectivity of the embolizations. In addition it may also reflect a better targeting effect with drug eluting beads since their distribution is more predictable than the distribution of an unstable emulsion/suspension such as the c-TACE injectable material. Finally, another difference with the results of Wigmore *et al.* is that half of their patients were treated for metastatic liver lesions that are known to be less hypervascular than HCC and therefore more prone to divert the administered material to the liver adjacent to the target lesion.

In our series one of the patients with PES developed an abscess. The relation of PES with infection has been well examined with c-TACE by Castells *et al.* (16) who prospectively studied 61 consecutive patients randomized in two groups with and without the administration of antibiotic prophylaxis. They found that 32% of their patients allocated in the antibiotic group and 34% of the group without prophylaxis developed fever >380°C none of which developed an infection (16). They also found no significant differences regarding the fever duration and the mean temperature between the two groups. Similarly they found a nearly significant correlation of PES with extent of tumor necrosis ($p<0.005$), reduction of tumor diameter >50% from the baseline or with the hospital stay (16).

The size of the beads did not correlate with a statistical significance with PES incidence overall, neither with the duration of fever or pain. This finding is in accordance with the results of a previous study that proved that beads of 100-300μm in diameter are not associated with increased rates of complications (6).

In conclusion PES is not a significant consideration post DEB-DOX, it does not indicate inadvertent embolization and reflects tumour necrosis.

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TABLE 1. Patient profile and tumor size.

Variables	
Age (mean±SD)	69.9±5.9 (range 46-82)
Gender	
Male	175 (73.8%)
Female	62 (26.2%)
Aetiology	
HBV	129 (54.4%)
HCV	35 (14.8%)
HBV + HCV	68 (28.7%)
Others	5 (2.1%)
Child stage	
A	116 (48.9%)
B	121 (51%)
Tumor/s diameter (mean±SD)	6.9±2.5 (range 3-14)

TABLE 2. Distribution of fever and pain by Bead size (Size in μm: S1=100-300, S2=100-300 and 300-500, S3=100-300 and 300-500 plus additional Bead Block).

Complication	EMBO 1 (n 237)			EMBO 2 (n 221)			EMBO 3 (n 189)			Total		
Bead Size	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Fever	38 (19.3%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
n	55	102	61	60	103	55	54	88	49	183	293	165
Total observations	197 (p=0.3)			218			101			n 641 (p=0.26)		
Pain	50 (25.3%)	67 (34%)	46 (23.4%)	4 (1.8%)	30 (13.5%)	33 (14.9%)	18 (9.5%)	39 (20.5%)	27 (14.2%)	60 (9.9%)	136 (22.3%)	106 (17.4%)
n	56	85	57	60	106	56	53	88	49	168	279	162
Total observations	198 (p=0.09)			222 (p<0.0001)			190 (p=0.098)			n 609 (p<0.0001)		

TABLE 3. Distribution of fever and pain by extent of embolization during the 3 scheduled sessions Type of embolization: SS: sub-segmental, S: segmental, >S: more than 2 segments.

Complication	EMBO 1 (n 237)			EMBO 2 (n 221)			EMBO 3 (n 189)			Total		
Embo Type	SS	S	>S	SS	S	>S	SS	S	>S	SS	S	>S
Fever	21 (10.8%)	81 (41.8%)	46 (23.7%)	2 (0.9%)	33 (15%)	3 (1.4%)	0 (0%)	2 (1.1%)	3 (1.6%)	0 (0%)	6 0.9%)	10 (1.6%)
n	31	104	59	35	126	55	26	120	43	99	372	163
Total observations	194 (p=0.49)			220 (p<0.0001)			187 (p<0.0001)			601 (p<0.0001)		
Pain	26 (13.3%)	104 (53.3%)	56 (28.7%)	32 (14.5%)	101 (41.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 0%)	1 (0.2%)
n	31	105	59	35	126	55	26	119	43	99	372	162
Total observations	195 (p=0.005)			220 (p=0.015)			189 (p=0.001)			604 (p=0.006)		

FIGURE 1A. Duration of fever (in days) correlated with baseline diameter of tumor in quartiles. (1^{st}: <5cm, 2^{nd}: 5-6cm, 3^{rd}: 6-8cm, 4^{th}: >8cm); p=0.02.

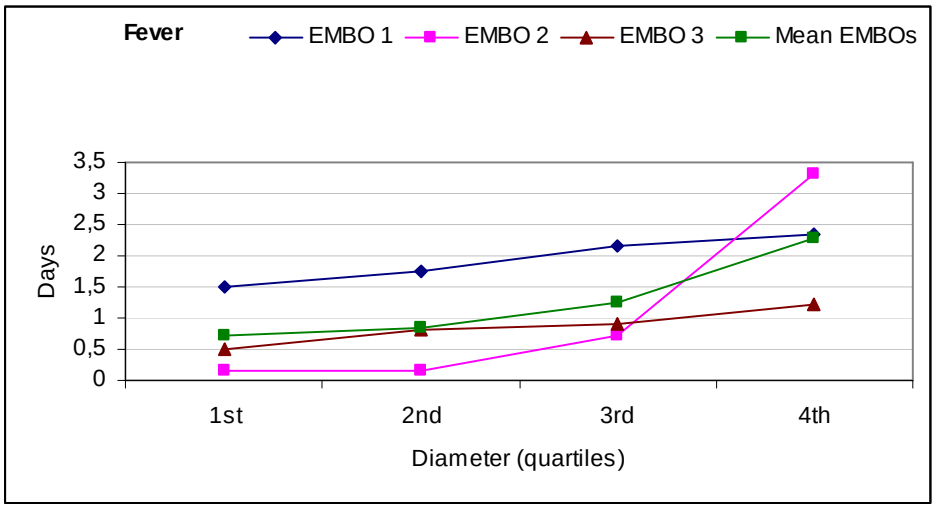

FIGURE 1B. Duration of pain (in days) correlated with diameter of lesion in quartiles.

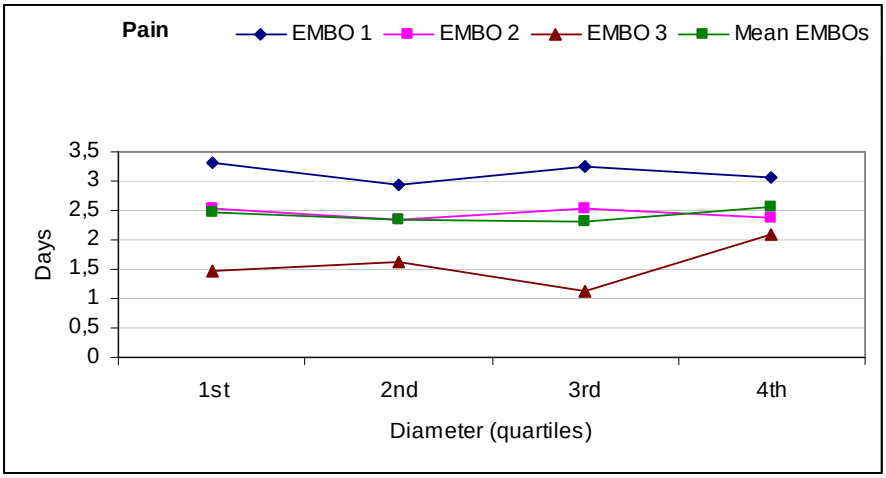

FIGURE 2A. Duration of fever correlated by bead diameter; *p*=0.009.

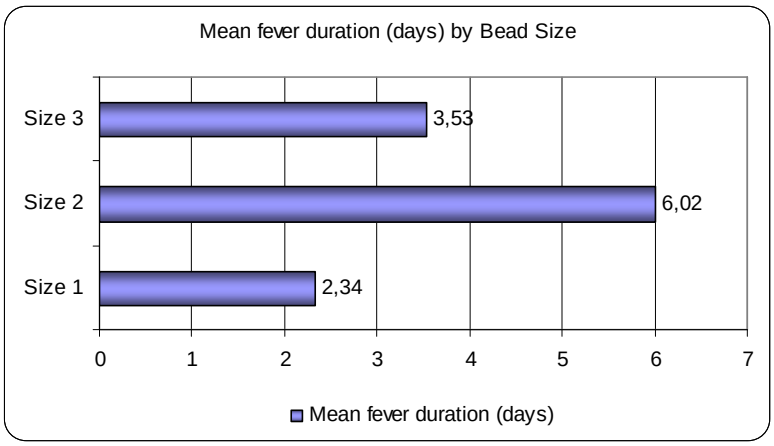

FIGURE 2B. Duration of fever correlated by extent of embolization; *p*=0.008.

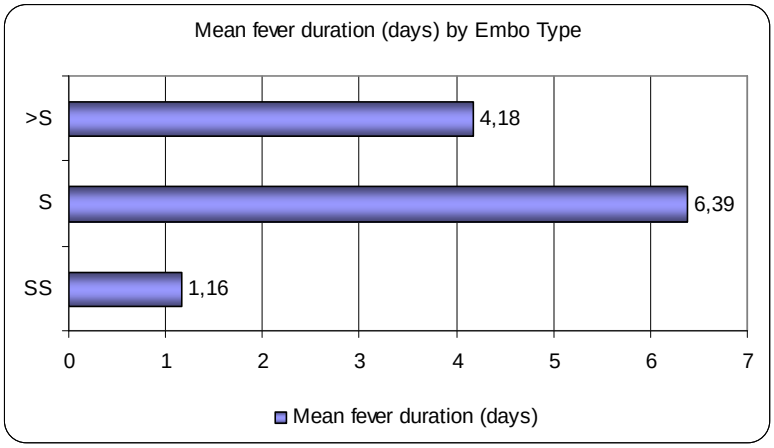

FIGURE 3A. AST levels during PES.

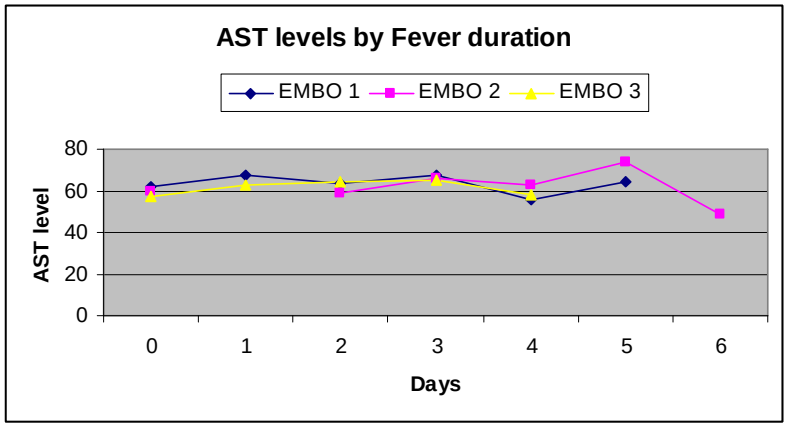

FIGURE 3B. ALT levels during PES.

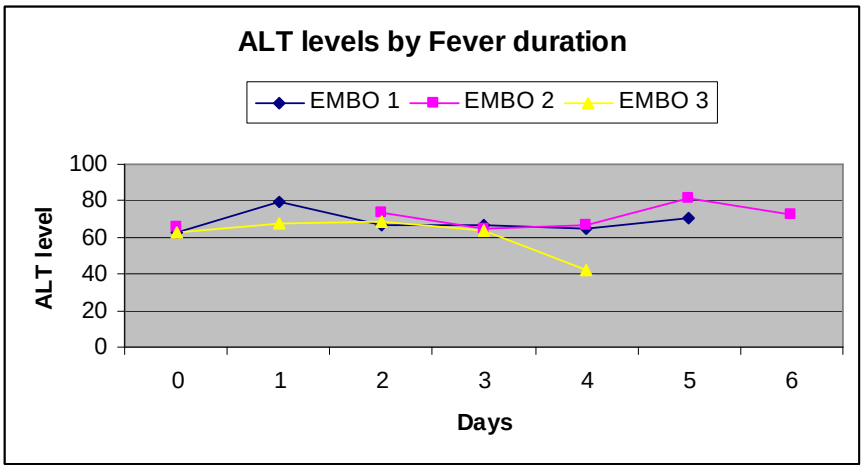

FIGURE 4A. PES severity (severe/grade: 2 requiring systematic analgetics; mild/grade 1: only symptomatic treatment) correlated by bead diamet; *p*=0.019.

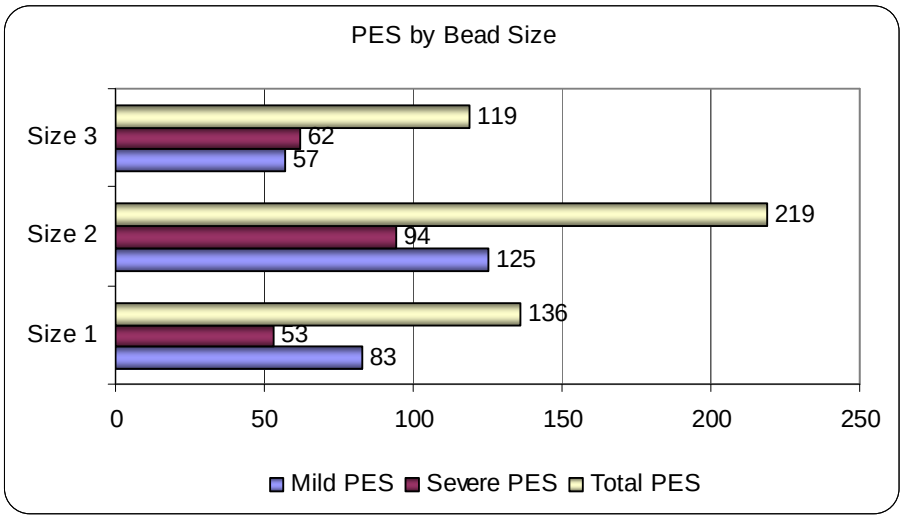

FIGURE 4B. PES severity correlated by extent of embolization; *p*=0.001.