ORIGINAL PAPER

Surg. Gastroenterol. Oncol. 2024;29(1):37-43 DOI: 10.21614/sgo-635

Determining Risk Factors for Post-Embolization Syndrome in Patients Undergoing TACE for Hepatic Malignancies

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is a major global health concern, particularly in developing countries. Trans-catheter arterial chemoembolization (TACE) is a widely accepted nonsurgical treatment for unresectable HCC, but it is often accompanied by postembolization syndrome (PES), characterized by fever, nausea, and abdominal pain. This study aims to investigate the factors influencing the development of PES in TACE-treated patients.
Methods: This prospective cohort study included 51 patients with histologically confirmed HCC undergoing TACE. Patients were followed up for 2 weeks post-TACE with evaluations at 24 hours, 72 hours, 1 week, and 2 weeks to assess for symptoms of PES. Risk factors like patient demographics, tumor characteristics, and treatment specifics were analyzed for their association with PES.
Results: The study found no significant correlation between PES and patient age, gender, or underlying liver disease. However, a higher dose of doxorubicin and the use of super-selective chemoembolization were significantly associated with the occurrence of PES. Interestingly, patients achieving complete remission showed a higher incidence of PES compared to those with partial remission, though this observation was not statistically significant in isolation.
Conclusion: This study emphasizes the significance of treatment-related factors over patient demographics in predicting PES following TACE in HCC patients. It highlights the need for careful consideration of doxorubicin dosing and chemoembolization techniques to mitigate PES risk, underscoring the complexity of managing TACE in HCC treatment. Further research is needed to fully understand the implications of remission status on PES.
Key words: hepatocellular Carcinoma (HCC), transarterial chemoembolization (TACE), post-embolization syndrome (PES)

Abbreviations:
HCC: hepatocellular carcinoma;
TACE: transarterial chemoembolization;
PES: postembolization syndrome;

INTRODUCTION

Hepatocellular carcinoma (HCC) is regarded as the fifth most frequent cancer in the world, with half to one million new cases identified each year (1). HCC is two to three times more common in developing countries than in developed

Received: 17.12.2023
Accepted: 14.02.2024

countries (2). HCC kills between 500,000 and 600,000 people annually, making it the second-highest cause of cancer-related deaths (3).

Trans-catheter arterial chemoembolization (TACE) is the intra-arterial injection of emulsified chemotherapeutic agents that mainly include gelatin, iodized oil, and cytotoxic agents (4). It has already been recognized as the preferred nonsurgical therapeutic option for unrespectable primary HCC and liver metastases by means of selectively delivering the chemotherapeutic agents to the targeted tumor area (5,6). In addition, it can target multiple lesions of HCC in a single treatment session and can be repeatedly applied to the same patient (7).

The most prevalent complication is PES, which is described as a syndrome that develops 1-3 days after TACE and is marked by fever, nausea and/or vomiting, stomach discomfort, and other symptoms (8,9). Although the period of PES is self-limiting, a significant study has revealed that 80%-90% of patients have PES after TACE and have a longer hospital admission (8). Furthermore, PES provides a negative treatment experience to patients who are experiencing TACE for the first time (10). The exact cause of PES is unknown, however intrahepatic and extrahepatic inflammation after cytotoxicity and cancer necrosis are thought to be involved (11).

Several studies have looked into the determinants of PES after TACE and found that prior PES, the size of cancer, the number of addressed tumor lumps, and the administration of a drug-eluting embolic agent are all important predictors (12-14).

The purpose of this study is to investigate the factors that influence the development of PES, the causal connection between them, and to establish which factors are risk or preventive factors for PES in TACE-treated patients.

MATERIAL AND METHODS

Study design and population

A prospective cohort follow-up' analytical study was conducted at Ibn Sina Teaching Hospital and Warith General Hospital, Baghdad from early November 2022 to the end of June 2023. The study included 51 individuals with histologically confirmed HCC who underwent TACE. A Sentinel lymph node biopsy was not done (unavailable).

Exclusion criteria

We excluded patients with previous TACE or embolization, other cancer types, liver transplantation, serious coexisting conditions, incomplete data, pregnancy, limited life expectancy, non-hepatocellular carcinoma, treatment outside of study site, non-compliance, age limitations, advanced disease stage, other liver diseases, concurrent treatments, inadequate liver function, infiltrative tumor growth, multiple TACE sessions, inadequate follow-up period, technical issues during TACE.

Patient follow-up

All patients were regular follow-ups for 2 weeks post-TACE for assessment of PES. During the follow-up period, patients had been assessed at specific time points to track their condition and any potential symptoms of PES:

- 24 Hours Post-TACE: Initial assessment within the first 24 hours to monitor for immediate post-procedure complications and symptoms.
- 72 Hours Post-TACE: Subsequent assessment to track early signs of PES and other related symptoms.
- 1 Week Post-TACE: Comprehensive assessment around the first week to capture the peak occurrence of PES symptoms and evaluate their severity.
- 2 Weeks Post-TACE: Final follow-up to identify any lingering or delayed symptoms and to assess the overall resolution of PES.

At each follow-up time point, an abstractor conducted assessments including:

- Symptom Evaluation: Patients would be interviewed and examined for symptoms such as fever, pain, nausea, vomiting, and discomfort.
- Clinical Examinations: Physical examinations might be performed to evaluate abdominal tenderness, vital signs, and any signs of infection or complications.
- Laboratory Tests: Blood tests could be conducted to measure markers of inflammation, liver function, and any changes related to the TACE procedure.

Patient privacy and informed consent are essential in this study. Patients had been informed about the follow-up process, the purpose of data collection, and their rights as research participants.

Table 1 - Age, gender, and underlying disease data distribution among the studied groups

Variables		PES (positive) (No.33)	PES (negative) (No.18)	P value
Age (years) (Mean ±SD)	52.27± 13.48	59.33±9.24	0.056	
Gender	Male	12 (36.4%)	9 (50.0%)	0.344
	Female	21 (63.6%)	9 (50.0%)	
Underlying disease	None	24 (72.7%)	12 (66.7%)	0.190
	HCV	2 (6.1%)	4 (22.2%)	
	Liver disease + HCV	7 (21.2%)	2 (11.1%)	

Primary end-point

To determine the risk factors of PES in patients with HCC following TACE such as patient age, tumor size, liver function, or the type of chemoembolization agents used.

Secondary endpoint

To identify the incidence and severity of PES, to assess the impact of PES on patients' quality of life, including pain levels, physical functioning, and overall well-being post-TACE.

Ethical considerations

Ethical approval was obtained from the institutional review board of both participating hospitals (no. 102 and 3380). Informed consent was obtained from all study participants before enrollment. Patient confidentiality and data privacy were maintained throughout the study.

Data collection

The information collected during each follow-up visit had been accurately recorded in the patient's medical records and the study database. This data had been used for analysis to determine the severity of PES symptoms and to identify potential risk factors contributing to PES.

Statistical analysis

In the data analysis of this study, the SPSS version 23 (IBM, NY, US) was used. The chi- square test and independent sample t test had been used to ass the significancy of the the difference between the two groups, and p value <0.05 was considered the statistical significnacnt value at CI 95%.

RESULTS

The *table 1* present the comparison of age, gender, and underlying disease between groups with positive and negative post-embolization syndrome (PES). The age difference between the groups is not statistically significant (p=0.056), with the positive group being younger on average. Gender distribution does not significantly differ between the groups either (p=0.344), with both genders fairly represented. Underlying disease prevalence, including HCV and liver disease (*figs. 1, 2*, 3), also does not show a significant association with PES outcomes (p=0.190). These findings suggest that age, gender, and presence of HCV or liver disease are not

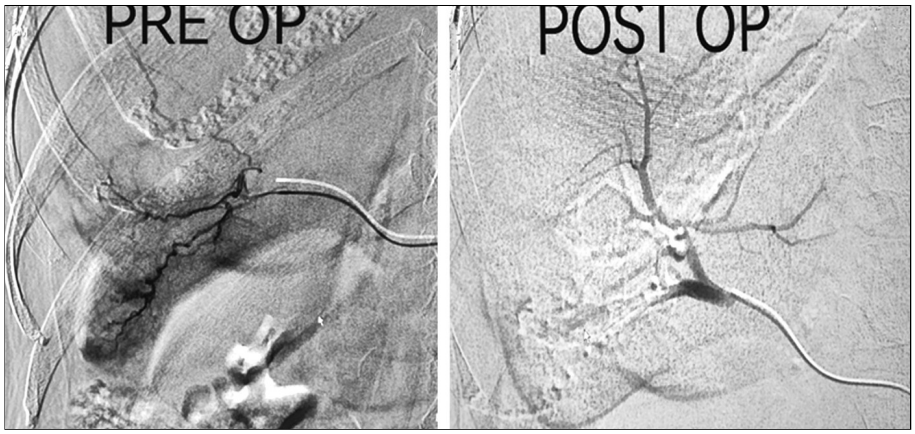

Figure 1 - 42-years-old female with history of peripheral hepatic cholangiocarcinoma, had blood supply from replace right hepatic artery from SMA, (pre and post trans-arterial chemo-embolization)

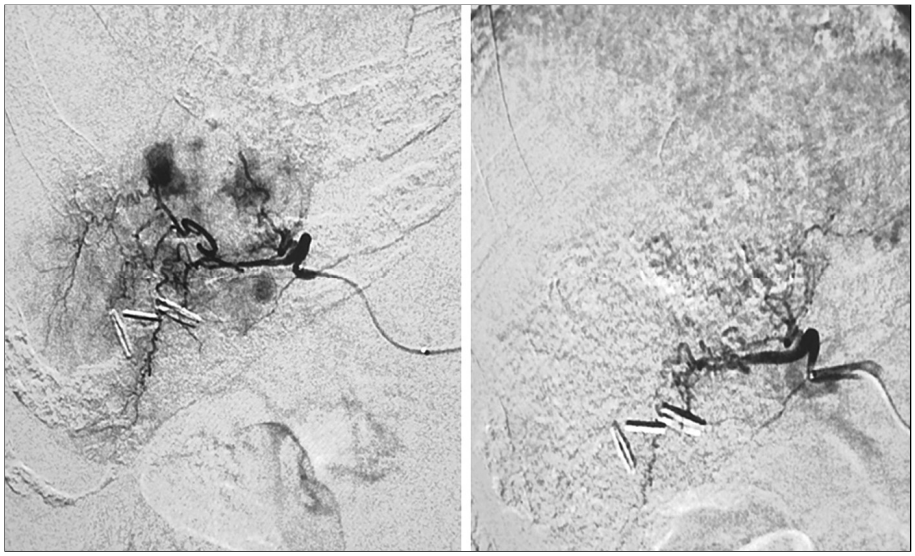

Figure 2 - 68-years-old female, she is a known case of virus C hepatitis with subsequent liver cirrhosis and 2 bilateral hepatic mass lesions, radiologically character of HCC with history of TACE (left--preembolization; right -post embolization)

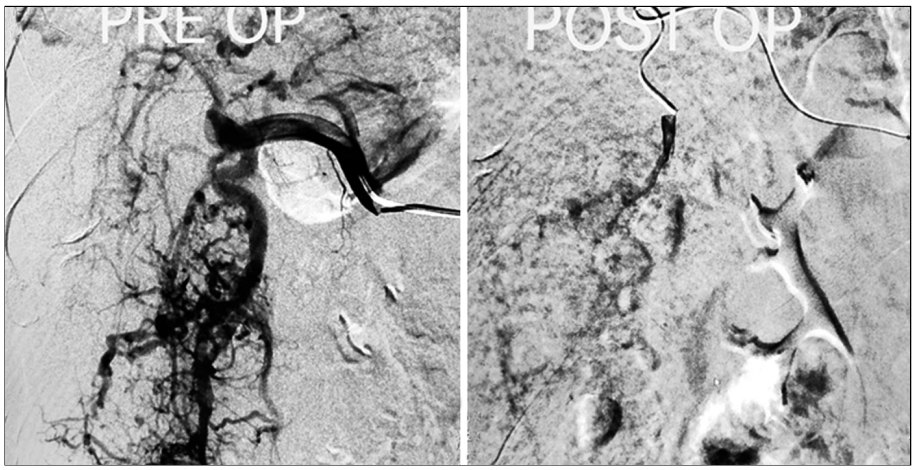

Figure 3 - 50-years-old male with hepatocellular carcinoma, admitted for embolization of the right hepatic artery

significant predictors of PES in this sample.

The *table 2* reveal insights into the risk factors associated with Post-Embolization Syndrome (PES). Notably, there's no significant correlation between PES and tumor size or number. However, a higher dose of doxorubicin is linked to PES (p=0.035). The presence of

Table 2 - Several risks parameters for the occurrence of PES

Variables		PES (positive) (No.33)	PES (negative) (No.18)	P value
Tumor size (Mean ±SD)	63.85±21.41	58.56±13.31	0.346	
Tumor number	1	21 (63.6%)	11 (61.1%)	0.961
	2	4 (12.1%)	2 (11.1%)	
	3	8 (24.2%)	5 (27.8%)	
Dose of doxorubicin (mg) (Mean ±SD)	65.61±10.95	58.61±11.08	0.035	
Albumin (g/L) (Mean ±SD)	42.09±4.75	42.39±4.36	0.827	
AFP	Normal	21 (63.6%)	12 (66.7%)	0.829
	High	12 (36.4%)	6 (33.3%)	
TSB ((Mean ±SD)	1.32±0.556	1.83±1.88	0.168	
Super selective chemoembolization	Presence	26 (78.8%)	9 (50.0%)	0.034
	Absence	7 (21.2%)	9 (50.0%)	
Child-Pugh score	A	28 (84.8%)	16 (88.9%)	0.689
	B	5 (15.2%)	2 (11.1%)	
Remission status	Complete remission	19 (57.6%)	0 (0.0%)	<0.001
	Partial remission	14 (42.4%)	18 (100.0%)	

Table 3 - Logistic regression test of the associated risk factors

Variables	Coefficient regression (B)	Odd ratio	Standard error	P value
Dose of doxorubicin	0.057	1.059	0.028	0.039
Super selective chemoembolization	1.312	3.714	0.635	0.038
Remission status	21.454	29.14	9.22	0.998

super-selective chemoembolization significantly increases PES risk (p=0.034). Most strikingly, positive PES was mostly experienced among those with complete remission rather than partial, while all patients with negative PES were from partial remission (p < 0.001). These findings underscore the importance of optimizing doxorubicin dosing, considering chemoembolization techniques, and striving for complete remission to mitigate PES risk in clinical practice.

In the logistic regression analysis presented *table 3*, we can observe the impact of several variables on the likelihood of Post-Embolization Syndrome (PES) occurrence, firstly the dose of doxorubicin, an increase in the dose of doxorubicin is associated with a statistically significant increase in the odds of experiencing PES (Coefficient B = 0.057, Odds Ratio = 1.059, p = 0.039), secondly, the Super-selective chemoembolization, patients who undergo super-selective chemoembolization have higher odds of developing PES (Coefficient B = 1.312, Odds Ratio = 3.714, p=0.038), and lastly the remission status, surprisingly, the coefficient for remission status is high (Coefficient B = 21.454), but the p-value is 0.998, indicating that it may not be a significant predictor of PES when considered in isolation. Further investigation or a larger sample size may be needed to clarify its role. In summary, this logistic regression analysis suggests that doxorubicin dosing and the use of super-selective chemoembolization are important factors to consider in managing PES risk. However, the role of remission status in predicting PES warrants further investigation.

DISCUSSION

Post-embolization syndrome (PES) is the most common adverse event following transarterial chemoembolization (TACE), affecting 60% to 80% of patients with hepatocellular carcinoma (HCC) (15). It is characterized by symptoms including fever, nausea, vomiting, malaise, and pain in the right upper quadrant, that were reported to extend up to two weeks (16). While the exact cause of PES remains unknown; it is widely considered to be multifactorial in nature. A common hypothesis suggests that the syndrome results from a combination of therapeutic cytotoxicity, tumor ischemia, as well as both intrahepatic and extrahepatic inflammation (11). However, existing literature does not provide specific guidelines for detection or prevention of PES in patients undergoing TACE.

Findings of this study reveal a complex interplay of factors influencing the development of PES. Notably, traditional predictors such as age, gender, and the presence of Hepatitis C Virus (HCV) or underlying liver disease did not emerge as significant contributors to PES. This observation supports the findings of Arslan et al. from a retrospective analysis conducted on 163 TACE patients between 2012 and 2018. They found no significant correlation between age, gender, presence of ascites and the development of PES (17). Contrarily, Mariana et al. found that female gender is a risk factor for development of PES in TACE treated HCC patients (14). Concerning underlying liver disease, a comprehensive study involving 954 patients treated with TACE for HCC by Roehlen et al. (18) found that the presence of liver cirrhosis was protective against PES, while the absence of liver cirrhosis emerged as a predictor of severe PES, contradicting this study. Furthermore, an absence of a significant correlation between PES and tumor size or number was found in this study. In contrast, Arslan et al. (17) reported that a tumor measuring over 5 cm and the treatment of more than one tumor increased the risk of developing PES following TACE. Moreover, Roehlen et al. (18) identified the largest tumor diameter as the strongest independent predictor of PES. They also observed that a larger tumor size was associated with a poorer prognosis. Mariana et al. also found that the size of the largest nodule treated is linked to PES development (14).

Up to date, there is no established optimal dosage for doxorubicin in TACE procedures (19). In this study, it was found that a higher dose of doxorubicin was significantly associated with the occurrence of PES, suggesting that medication management could be a key area for reducing PES risk. Several previous studies have similarly demonstrated that a higher dose of chemoembolization agents is correlated with an increased risk of PES (20-22). This is expected, considering that the chemotherapeutic agent used in TACE plays a role in the pathogenesis of post-embolization syndrome PES. This involvement is attributed to both the inherent toxicity of the drug and the anti-inflammatory response it elicits (11). Moreover, Bessar et al. compared the use

of low dose of doxorubicin (50 mg) versus the commonly used dose (100 mg) for TACE in HCC patients. They found that low dose doxorubicin is not only associated with fewer PES symptoms, but also had no effect on patient's survival or tumor response (19).

Additionally, in this study, the use of super-selective chemoembolization significantly increased the risk of PES. In this technique, a catheter is positioned as distal as possible and close to the tumor, targeting smaller and more specific regions of the liver to maximize the anti-tumoral effect, and minimize the collateral damages of the surrounding liver parenchyma (23). The increased risk of PES observed in this study could be due to a more concentrated effect of chemotherapeutic agents in a localized area, leading to a more pronounced inflammatory response. Studies have shown that TACE can induce a systemic inflammatory response and elevation of cytokines levels (24), which is a key factor in the pathogenesis of PES. However, Arslan et al. found that not performing TACE in a super-selective manner is associated with an increased risk of PES (17). Lastly, PES was observed to be more common among patients achieving complete remission than those with partial remission, in this study. This might be explained by the fact that TACE destroys tumor cells by inducing subsequent necrosis (25). Therefore, complete tumor necrosis, which is more likely in cases of complete remission, might release more tumor antigens and inflammatory mediators, that can trigger a systemic inflammatory response. However, given the high p-value (0.998), this observation suggests that while there might be an association, it is not statistically significant when considered in isolation. This specific aspect of the findings requires further exploration, potentially with a larger sample size, as it has not been mentioned in the existing literature.

Limitations of the study

This study included a potentially small sample size, which may limit the statistical power to detect significant associations, particularly regarding the relationship between remission status and PES. The single-center design may affect the generalizability of the findings across different patient populations and treatment settings. Additionally, the study did not account for all possible confounding variables, such as specific liver function parameters and previous treatments, which could influence PES development. Finally, the cross-sectional nature of the study precludes conclusions about long-term outcomes and causal relationships.

CONCLUSION

In this study, it was found that patient demographics (age, gender), Hepatitis C Virus (HCV) infection, liver disease, tumor size, and number are not significant predictors of PES. However, a higher dose of doxorubicin, the use of super-selective chemoembolization and complete remission are associated with an increased risk of PES. Nevertheless, further exploration is essential in case of remission state, as this observation may not hold as a significant predictor on its own.

Conflicts of interest

The authors declared no potential conflicts of interest.

REFERENCES

1. Kim HY, Kim CW, Choi JY, Park C-H, Lee CD, Yim HW. A decade-old change in the screening rate for hepatocellular carcinoma among a hepatitis B virus-infected population in Korea. Chin Med J (Engl). 2016;129(1):15-21.
2. Nawawi O, Hazman MN, Abdullah BJJ, Vijayananthan A, Manikam J, Mahadeva S, et al. Transarterial embolisation of hepatocellular carcinoma with doxorubicin-eluting beads: single centre early experience. Biomed Imaging Interv J. 2010;6(1):e7.
3. Xu X-S, Chen W, Miao R-C, Zhou Y-Y, Wang Z-X, Zhang L-Q, et al. Survival analysis of hepatocellular carcinoma: A comparison between young patients and aged patients. Chin Med J (Engl). 2015;128(13):1793-800.
4. Morshid A, Elsayes KM, Khalaf AM, Elmohr MM, Yu J, Kaseb AO et al. A machine learning model to predict hepatocellular carcinoma response to transcatheter arterial chemoembolization. Radiol Artif Intell. 2019;1(5):e180021.
5. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut. 2020; 69(8):1492-1501.
6. Roxburgh P, Evans TRJ. Systemic therapy of hepatocellular carcinoma: are we making progress? Adv Ther. 2008;25(11): 1089-104.
7. Couri T, Pillai A. Goals and targets for personalized therapy for HCC. Hepatol Int. 2019;13(2):125-137.
8. Blackburn H, West S. Management of postembolization syndrome following hepatic transarterial chemoembolization for primary or metastatic liver cancer. Cancer Nurs. 2016;39(5):E1-E18.
9. Rmilah AA, Qrareya MN, Fleming C, Alkurashi AK, Nyberg S, Leise M, et al. Association of cirrhosis and other patient and procedural characteristics with postembolization syndrome after bland hepatic artery embolization for hepatic malignancy. AJR Am J Roentgenol. 2022;218(6):1030-1039.
10. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387-95.
11. Dhand S, Gupta R. Hepatic transcatheter arterial chemoembolization complicated by postembolization syndrome. Semin Intervent Radiol. 2011;28(2):207-11.
12. Arslan M, Degirmencioglu S. Risk factors for postembolization syndrome after transcatheter arterial chemoembolization. Curr Med Imaging Rev. 2019;15(4):380-385.

13. Khalaf MH, Sundaram V, AbdelRazek Mohammed MA, Shah R, Khosla A, Jackson K. et al. A predictive model for postembolization syndrome after transarterial hepatic chemoembolization of hepatocellular carcinoma. Radiology. 2019;290(1):254-261.
14. Lima M, Dutra S, Gomes FV, Bilhim T, Coimbra É. Risk factors for the development of postembolization syndrome after transarterial chemoembolization for hepatocellular carcinoma treatment. Acta Med Port. 2018;31(1):22-29.
15. Jun CH, Ki HS, Lee HK, Park KJ, Park SY, Cho SB, et al. Clinical significance and risk factors of postembolization fever in patients with hepato-cellular carcinoma. World J Gastroenterol. 2013;19(2): 284-9.
16. Blackburn H, West S. Management of Postembolization Syndrome Following Hepatic Transarterial Chemoembolization for Primary or Metastatic Liver Cancer. Cancer Nurs. 2016;39(5):E1-E18.
17. Arslan M, Degirmencioglu S. Risk Factors for Postembolization Syndrome After Transcatheter Arterial Chemoembolization. Curr Med Imaging Rev. 2019;15(4):380-385.
18. Roehlen N, Stoehr F, Müller L, Luxenburger H, Gairing SJ, Reincke M, et al. Prediction of postembolization syndrome after transarterial chemoembolization of hepatocellular carcinoma and its impact on prognosis. Hepatol Commun. 2023;7(10):e0252.
19. Bessar AA, Farag A, Abdel Monem SM, Wadea FM, Shaker SE, Ebada MA, et al. Transarterial chemoembolisation in patients with hepatocellular carcinoma: low-dose doxorubicin reduces post-embolisation syndrome without affecting survival - prospective interventional study. Eur Radiol Exp. 2021;5(1):1-10.
20. He JJ, Yin XX, Wang T, Chen MY, Li XL, Yang XJ, et al. Factors influencing postembolization syndrome in patients with hepatocellular carcinoma undergoing first transcatheter arterial chemoembolization. J Cancer Res Ther. 2021;17(3):777-83.
21. Leung DA, Goin JE, Sickles C, Raskay BJ, Soulen MC. Determinants of postembolization syndrome after hepatic chemoembolization. J Vasc Interv Radiol. 2001;12(3):321-6.
22. Li C-P, Chao Y, Chen L-T, Lee R-C, Lee W-P, Yuan J-N, et al. Fever after transcatheter arterial chemoembolization for hepatocellular carcinoma: incidence and risk factor analysis. Scand J Gastroenterol. 2008;43(8):992-9.
23. de Baere T, Ronot M, Chung JW, Golfieri R, Kloeckner R, Park JW, et al. Initiative on superselective conventional transarterial chemoembolization results (INSPIRE). Cardiovasc Intervent Radiol. 2022;45(10):1430-1440.
24. Chao Y, Wu C-Y, Kuo C-Y, Wang JP, Luo J-C, Kao C-H, et al. Cytokines are associated with postembolization fever and survival in hepatocellular carcinoma patients receiving transcatheter arterial chemo-embolization. Hepatol Int. 2013;7(3):883-92.
25. Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol. 2002;13(9 Pt 2):S211-21.