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ORIGINAL RESEARCH

Risk Factors and Predictive Analysis of Acute Severe Abdominal Pain After Hepatic Artery Infusion Chemotherapy in Patients with Hepatocellular Carcinoma

Jinpeng Li[1,*], Congcong Shi[2,*], Jiao Chen[1], Yue Zhao[3], Jiasheng Du[4,*], Jinlong Song[1]

[1]Department of Interventional Therapy I, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, 250117, People's Republic of China; [2]Depression Disorder Diagnosis and Treatment Center, Shandong Mental Health Center, Jinan, Shandong, 250014, People's Republic of China; [3]Medical Imaging Technology Program, Qingdao Binhai University, Qingdao, 266000, People's Republic of China; [4]Department of Oncology, Linqing People's Hospital, Liaocheng, 252600, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jinpeng Li, Department of Interventional Therapy I, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Huaiyin District, Jinan, Shandong, 250117, People's Republic of China,
Tel +86 531-67626412, Email Ljpxxx308@126.com

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Purpose: To investigate the incidence patterns and risk factors of acute abdominal pain following hepatic arterial infusion chemotherapy (HAIC) in liver cancer patients and develop a preliminary prediction model for post-HAIC abdominal pain.

Patients and Methods: Four hundred hepatocellular carcinoma patients who underwent HAIC at the Affiliated Cancer Hospital of Shandong First Medical University from January 2021 to March 2023 were retrospectively analyzed. The patients were categorized into two groups (abdominal pain and no abdominal pain) based on the occurrence of acute moderate to severe abdominal pain within 24 h after HAIC. Univariate analysis was performed on data from the two groups. Statistically significant factors were subjected to logistic regression analysis to construct a preliminary prediction model, and the predictive performance was evaluated.

Results: A total of 358 hAIC procedures were performed in 242 patients who met the inclusion criteria. Of the 242 eligible patients, 88 (36.4%) experienced moderate to severe abdominal pain, while 154 (63.6%) had no significant pain. Age, tumor diameter, distance between the tumor and liver capsule, presence of portal vein tumor thrombus, oxaliplatin preparation time, and oxaliplatin manufacturer were independent predictors of acute moderate to severe abdominal pain following HAIC. The final prediction model demonstrated good predictive ability with an area under the receiver operating characteristic curve of 0.795 (95% confidence interval: 0.740–0.853).

Conclusion: The model developed in this study effectively predicted the risk of acute moderate to severe abdominal pain following HAIC and may provide a basis for more precise prevention and intervention strategies in clinical practice.

Keywords: hepatocellular carcinoma, hepatic arterial infusion chemotherapy, abdominal pain, risk factors

Introduction

Hepatocellular carcinoma (HCC) represents a significant global health burden, ranking as the sixth most prevalent malignancy worldwide and the third leading cause of cancer-related mortality.[1] The insidious nature of the onset of HCC, coupled with challenges in early detection, results in 25–70% of patients being initially diagnosed at intermediate to advanced stages, thereby precluding curative surgical interventions; the median survival time in such cases is dismal, ranging from 4.2 to 7.9 months.[2] Current evidence-based guidelines, both national and international, recommend systemic therapies, such as sorafenib or lenvatinib, or locoregional treatments, like transcatheter arterial chemoembolization (TACE), as first-line management strategies for intermediate to advanced HCC.[3,4] However, the long-term efficacy

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of these therapeutic modalities remains suboptimal. Consequently, there is an urgent need to explore more effective treatment approaches and strategies to improve the prognosis of patients with advanced HCC.

The liver's unique dual blood supply system is characterized by the perfusion of the normal hepatic tissues by the portal vein, while approximately 90% of the blood supply to HCC lesions is derived from the hepatic artery.[5] Hepatic arterial infusion chemotherapy (HAIC) has emerged as a pivotal interventional treatment modality for HCC, demonstrating remarkable therapeutic efficacy by maximizing antitumor effects while concurrently minimizing damage to normal hepatic parenchyma and reducing systemic toxicities.[6] HAIC offers several significant advantages over conventional intravenous chemotherapy: it facilitates the administration of high-concentration chemotherapeutic agents directly to the tumor site, enhancing local drug delivery; it significantly reduces the incidence of systemic toxicities, thereby improving treatment adherence and patient quality of life;[7] and it potentially overcomes tumor drug resistance mechanisms, leading to higher disease response rates and improved clinical outcomes. Thus, HAIC demonstrates the potential for managing HCC, particularly in patients with advanced tumor stages or those unable to undergo conventional therapies.

Despite the proven efficacy of HAIC in treating intermediate to advanced hepatocellular carcinoma, it is imperative to address the adverse reactions and complications associated with this treatment modality.[8] Acute abdominal pain is the most prevalent complication of HAIC, with some patients experiencing severe pain during arterial chemotherapy administration, which can significantly impede post-operative recovery; in severe cases, it may lead to treatment discontinuation or refusal of subsequent interventions.

Recent studies have demonstrated HAIC's therapeutic potential in advanced HCC treatment, particularly when combined with emerging therapeutic modalities. A meta-analysis by Yu et al revealed that combining HAIC with immunotherapy and anti-angiogenic agents yielded superior outcomes, achieving an objective response rate of 45.6% (95% CI: 35.2–56.4%).[9] The FOLFOX-based HAIC regimen has shown notable efficacy in unresectable HCC, with Lin et al reporting a median progression-free survival of 8.9 months and an objective response rate of 52.3% when integrated with targeted therapy and immunotherapy. However, treatment-related adverse events, particularly abdominal pain (reported in approximately 35% of patients), remain a significant clinical challenge.[10]

The successful implementation of HAIC necessitates rigorous safety protocols and standardized management strategies. Janczewski et al[11] demonstrated that while HAIC can be safely administered in specialized centers, optimal outcomes depend on careful patient selection and systematic complication management protocols. The pathophysiology of post-HAIC pain encompasses multiple mechanisms, including chemotherapy-induced vascular effects, inflammatory responses to tumor necrosis, potential ischemic complications, and individual pain sensitivity factors. Evidence suggests that implementing standardized pain management protocols, incorporating pre-emptive analgesia and optimized drug administration timing, can effectively mitigate post-HAIC pain complications.

The present study aimed to analyze the risk factors associated with moderate to severe abdominal pain after HAIC. The findings may provide valuable insights into implementing preventive pain management strategies, thereby improving treatment adherence and patient outcomes. The objective was to optimize the HAIC protocol by identifying and understanding the risk factors to minimize the adverse effects and maintain the therapeutic benefits in the management of advanced HCC.

Patients and Methods

Patients

Consecutive HCC patients treated with HAIC at the Affiliated Cancer Hospital of Shandong First Medical University from January 2021 to March 2023 were retrospectively analyzed (Figure 1). The inclusion criteria were as follows: a diagnosis of primary HCC confirmed by clinical and/or pathological examination;[12] age >18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2; life expectancy >3 months; Child-Pugh class A or B liver function; and no significant preoperative pain symptoms or history of long-term analgesic use. The exclusion criteria included incomplete clinical data, concomitant malignancies of other types, and severe comorbidities prior to treatment.

This study was approved by the Institutional Ethics Review Board of Shandong Cancer Hospital and Institute, affiliated with Shandong First Medical University (Jinan, Shandong Province, China; (No. SDTHEC202408021). It was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for written informed consent

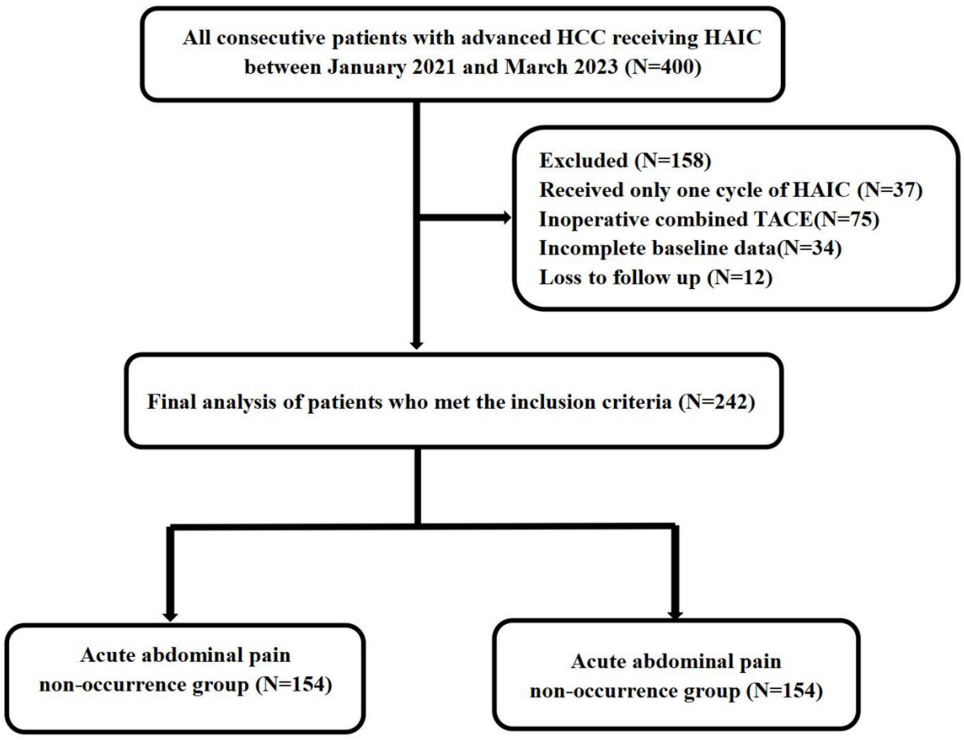

Figure 1 Flowchart Regarding Participant Selection Process.

was waived due to the retrospective nature of the study. This retrospective study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

Observation Indicators and Evaluation Criteria

The patients were stratified into two groups based on the occurrence of pain within 24 h post-HAIC: abdominal pain and no abdominal pain. Clinical data, encompassing the demographic characteristics (sex, age), disease-related factors (Barcelona Clinic Liver Cancer [BCLC] stage, tumor number, alpha-fetoprotein [AFP] level, and Child-Pugh classification), treatment-related factors (oxaliplatin manufacturer, oxaliplatin preparation time, diameter of the catheterized hepatic artery, and intra-arterial lidocaine application), and patient status (ECOG PS score), were collected and compared between the two groups. The variables were subjected to analysis to elucidate their potential influence on the occurrence of abdominal pain following HAIC in patients with HCC.

Pain intensity was evaluated using the Visual Analog Scale (VAS), a validated 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable).[13] The pain severity was categorized as follows: 0 (no pain), 1–3 (mild pain), 4–6 (moderate pain), and 7–10 (severe pain). VAS scores were recorded at 0, 2, 4, 6, 12, and 24 h after HAIC treatment. The highest score recorded during this 24-h period was utilized as the final pain score for subsequent analysis, providing a comprehensive assessment of the peak pain intensity experienced by each patient following the HAIC procedure.

HAIC Procedure

The HAIC protocols involved FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) with catheter placement through the femoral artery, and the procedures were comparable to those reported previously.[8,14] Intraoperatively, the gastroduodenal artery was embolized as required using a microspring coil, and the microcatheter was inserted into the principal blood supply artery of the tumor. All chemotherapeutic agents were infused via microcatheter arterial infusion using the following protocol: 85 or 130 mg/m^2 of oxaliplatin drip for 2 h, 400 mg/m^2 calcium folinic acid drip for 2 h, and 400 mg/

m^2 5 fluorouracil regimen followed by 2400 mg/m^2 continuous infusion for 46 h. The therapy was repeated every 3–4 weeks for a maximum of six cycles.

Statistical Analyses

SPSS 26.0 software was used for data analysis. Continuous variables conforming to normal distribution were expressed as the mean ± standard deviation and analyzed using the independent sample *t*-test. Continuous variables not conforming to normal distribution were expressed as the median and interquartile range and analyzed using the Mann–Whitney *U*-test. Categorical variables were analyzed using the χ^2 test. Initial comparisons between the abdominal pain and no abdominal pain groups were performed using Student's *t*-test for continuous variables and Chi-square test for categorical variables. Subsequently, univariate logistic regression analysis was conducted to identify potential risk factors associated with post-HAIC acute moderate to severe abdominal pain. Variables with $P < 0.05$ in the univariate analysis were then included in the multivariate logistic regression model. A logistic regression model was used to analyze the risk factors for acute moderate to severe abdominal pain after HAIC. A P-value of <0.05 was considered statistically significant.

Results

Patient Characteristics and Patterns of Abdominal Pain

A total of 242 eligible patients with intermediate to advanced HCC undergoing HAIC were enrolled in this study (Table 1). The cohort, comprising 188 males (77.7%) and 54 females (22.3%) with a mean age of 59.7 ± 11.3 years (range, 32–81 years), received an average of 2.46 ± 1.32 hAIC sessions (range, 1–8; total, 358 treatments). The number of patients in the two groups was as follows: 88 (36.4%) in the abdominal pain group and 154 (63.6%) in the no abdominal pain group. Moderate to severe abdominal pain onset was observed as early as 30 min after the procedure in 10 patients (11.36%), with a peak incidence between 6–12 h (n = 41, 46.59%), followed by a decline thereafter (n = 15, 17.05% after 12 h). Prophylactic analgesic treatment, primarily non-steroidal anti-inflammatory drugs, was administered to 214 patients (88.43%) after the procedure. Notably, intra-arterial lidocaine injection demonstrated high efficacy, providing pain relief in 97.19% (208 out of 214) of the patients.

Table 1 Baseline Characteristics of the Patients

Characteristics	No. (%)
Age (years)	59.70 ± 11.30
Sex (male), n (%)	188 (77.68%)
Hepatitis B virus infection	175 (72.31%)
Liver cirrhosis	152 (62.81%)
Number of HAIC sessions	2.46 ± 1.32
Total bilirubin (umol/L)	17.48 ± 7.25
Albumin (g/L)	39.21 ± 7.12
AFP > 400 (ng/mL)	162 (66.94%)
ECOG	
0	145 (59.92%)
1	97 (40.08%)
Child-Pugh grade, n (%)	
A	194 (80.17%)
B	48 (19.83%)
BCLC stage	
B	44 (18.18%)
C	198 (81.82%)
PVTT	
Yes	167 (69.01%)
No	75 (30.99%)

(*Continued*)

Table 1 (Continued).

Characteristics	No. (%)
OXA manufacturers	
Import	145 (59.92%)
Domestic	97 (40.08%)
OXA preparation time	
Less than 4 h	142 (58.68%)
More than 4 h	100 (41.32%)

Note: Data are expressed as n (%) or mean ± standard deviation.
Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; OXA, oxaliplatin.

Comparison Between Patients with and without Abdominal Pain Post HAIC

The comparison was conducted on the 242 patients, and the results are summarized in Table 2. No statistically significant difference in gender between the abdominal pain and no abdominal pain groups ($\chi 2 = 1.165$, $P = 0.280$). Similarly, the number of previous HAIC sessions did not differ significantly between the abdominal pain (2.68 ± 1.32) and no abdominal pain (2.96 ± 1.55) groups ($t = 1.425$, $P = 0.156$).

Furthermore, no statistically significant differences were observed between the two groups in terms of gender, history of hepatitis B, AFP levels, ECOG performance status, extrahepatic metastasis, or alanine transaminase levels. However, significant differences were noted in age, tumor diameter, tumor number, distance from tumor to liver capsule, presence of portal vein tumor thrombus (PVTT), oxaliplatin preparation time, oxaliplatin manufacturer, and hepatic artery diameter ($P < 0.05$).

Table 2 Comparison Between Patients With and Without Abdominal Pain Post HAIC (n = 242)

Characteristic	Without Pain (n = 154)	With Pain (n = 88)	Statistic Value	P
Age (years)			5.984[b]	0.014
>60	54 (35.06%)	45 (51.14%)		
≤60	100 (64.94%)	43 (48.86%)		
Gender			1.165[b]	0.280
Male	123 (79.87%)	65 (73.86%)		
Female	31 (20.13%)	23 (26.14%)		
BMI (kg/m^2)	22.06 ± 2.51	22.18 ± 2.49	−0.359[a]	0.720
Number of HAIC sessions	2.96 ± 1.55	2.68 ± 1.32	1.425[a]	0.156
Hepatitis			1.009[b]	0.315
No	46 (29.87%)	21 (23.86%)		
Yes	108 (70.13%)	67 (76.14%)		
Tumor diameter (cm)			4.939[b]	0.026
0~5	48 (31.17%)	40 (45.45%)		
≥5	106 (68.83%)	48 (54.55%)		
Distance from liver capsule (cm)			4.567[b]	0.033
0~1	30 (19.48%)	8 (9.09%)		
≥1	124 (80.52%)	80 (90.91%)		
PVTT			6.359[b]	0.012
Yes	115 (74.68%)	52 (59.09%)		
No	39 (25.32%)	36 (40.91%)		

(*Continued*)

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Table 2 (Continued).

Characteristic	Without Pain (n = 154)	With Pain (n = 88)	Statistic Value	P
Tumor number			9.518[b]	0.002
1~	98 (63.64%)	45 (51.14%)		
3~	56 (36.36%)	43 (48.86%)		
ECOG PS			1.662[b]	0.197
0	97 (62.99%)	48 (54.55%)		
1	57 (37.01%)	40 (45.45%)		
BCLC stage			1.165[b]	0.280
B	31 (20.12%)	23 (26.13%)		
C	123 (79.88%)	65 (73.87%)		
Child-Pugh grade			0.480[b]	0.488
A	128 (83.11%)	70 (79.55%)		
B	26 (16.89%)	18 (20.45%)		
AFP			0.067[b]	0.796
<400 ng/mL	50 (32.47%)	30 (34.09%)		
≥400 ng/mL	104 (67.53%)	58 (65.91%)		
OXA manufacturers			10.226[b]	0.001
Import	114 (74.03%)	31 (35.22%)		
Domestic	40 (25.97%)	57 (64.78%)		
OXA preparation time			13.695[b]	0.001
Less than 4 h	110 (71.43%)	32 (36.36%)		
More than 4 h	44 (28.57%)	56 (63.64%)		
Extrahepatic metastasis			0.500[b]	0.480
Yes	86 (55.84%)	45 (61.14%)		
No	68 (44.16%)	43 (48.86%)		
WBC ($\times 10^9$/L)	5.42 ± 1.58	5.33 ± 1.45	0.439[a]	0.661
PLT ($\times 10^9$/L)	138.48 ± 54.49	125.65 ± 45.69	1.865[a]	0.063
TBil (μmol/L)	18.63 ± 7.82	16.78 ± 5.85	1.931[a]	0.055
Albumin (g/dL)	40.36 ± 8.29	38.81 ± 6.78	1.492[a]	0.137
AST (U/L)	62.36 ± 9.47	58.13 ± 11.81	3.050[a]	0.003
Hepatic artery diameter (mm)	3.71 ± 0.42	4.32 ± 0.68	−0.826[a]	0.001
Post-operative Analgesics			4.923[b]	0.295
Flurbiprofen	34 (22.08%)	16 (18.18%)		
Morphine	23 (14.94%)	17 (19.32%)		
Dezocine	23 (14.94%)	21 (23.86%)		
Diclofenac	56 (36.36%)	24 (27.27%)		
No	18 (11.68%)	10 (11.37%)		

Notes: Data are expressed as n (%) or mean ± standard deviation. [a]t value, [b]X^2 value.

Abbreviations: BMI, body mass index; HAIC, hepatic arterial infusion chemotherapy; PVTT, portal vein tumor thrombus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; OXA, oxaliplatin; WBC, white blood cell; PLT, platelets; TBil, total bilirubin; AST, aspartate aminotransferase.

Multivariate Analysis of Acute Moderate to Severe Abdominal Pain After HAIC

Variables exhibiting statistical significance in the univariate analysis were incorporated into a multivariate logistic regression model. Table 3 delineates the resultant independent risk factors associated with acute moderate to severe abdominal pain following HAIC: age (odds ratio [OR] = 1.028, P = 0.031); tumor diameter (OR = 1.215, P = 0.007); distance from liver capsule (OR = 0.662, P = 0.029); PVTT (OR = 2.370, P = 0.030); oxaliplatin preparation time (OR = 1.160, P = 0.032); and oxaliplatin manufacture (OR = 2.038, P = 0.028).

For the multivariate analysis, continuous variables were dichotomized using clinically relevant cut-off points, and categorical variables were binary-coded as follows: age, >60 years (1) vs ≤60 years (0); tumor diameter, ≥5 cm (1) vs

Table 3 Multivariate Analysis of Acute Moderate to Severe Abdominal Pain After Hepatic Arterial Infusion Chemotherapy

Variables	β	SE	Wald χ^2	P-value	OR	95% CI
Constant	−2.876	1.053	7.456	0.006	0.056	-
Age (years)	0.028	0.013	4.638	0.031	1.028	1.002~1.055
Tumor diameter (cm)	0.195	0.072	7.324	0.007	1.215	1.055~1.399
Distance from liver capsule (cm)	−0.412	0.189	4.752	0.029	0.662	0.457~0.959
Portal vein tumor thrombus (yes vs no)	0.863	0.398	4.697	0.030	2.370	1.086~5.172
Oxaliplatin preparation time (>4h)	0.148	0.069	4.603	0.032	1.160	1.013~1.328
Oxaliplatin manufacturer (domestic vs imported)	0.712	0.324	4.826	0.028	2.038	1.080~3.847

<5 cm (0); distance from the liver capsule: ≥1 cm (1) vs <1 cm (0); PVTT, present (1) vs absent (0); oxaliplatin preparation time, >4 hours (1) vs ≤4 hours (0); oxaliplatin manufacture, domestic (1) vs imported (0). Based on the multivariate logistic regression analysis, a predictive model for post-HAIC acute moderate to severe abdominal pain was developed: logit (P) = $-2.876 + 0.228X_1 + 0.195X_2 - 0.412X_3 + 0.863X_4 + 0.148X_5 + 0.712X_6$.

Where P denotes the probability of developing acute moderate to severe abdominal pain, X_1 denotes the age, X_2 denotes the tumor diameter, X_3 is the distance from the liver capsule, X_4 denotes the PVTT, X_5 denotes the oxaliplatin preparation time, and X_6 denotes the oxaliplatin manufacturer.

Analysis of the Predictive Model for Acute Moderate to Severe Abdominal Pain Following HAIC

The predictive model's performance for acute moderate to severe abdominal pain following HAIC was evaluated using the receiver operating characteristic (ROC) curve, as illustrated in Figure 2. The area under the curve for the predictive model was 0.795 (95% CI, 0.740–0.853; P < 0.001). The optimal cut-off point was determined using the maximum Youden index (0.468), at which the model demonstrated a sensitivity of 76.8% and a specificity of 72.4%,

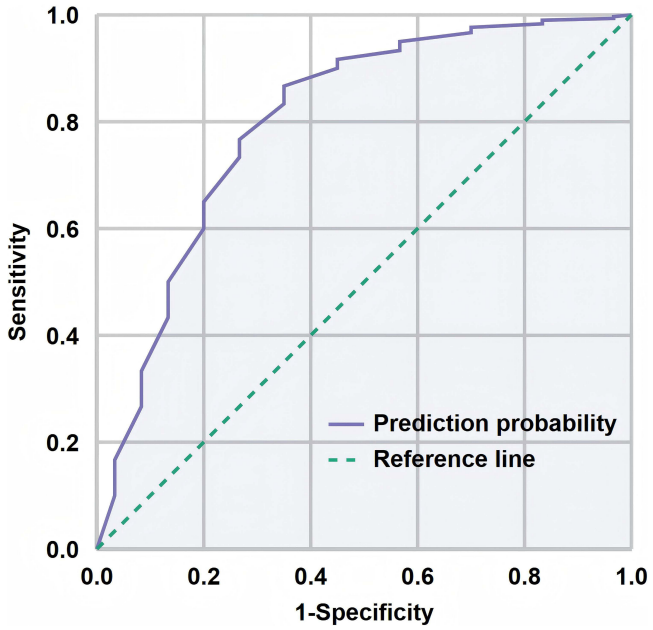

Figure 2 ROC Curve Evaluation of the Predictive Model's Performance for Acute Moderate to Severe Abdominal Pain after HAIC.

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indicating good predictive performance. A Hosmer-Lemeshow test χ^2 of 1.795 (P = 0.241) suggested an adequate model fit.

Discussion

In managing intermediate and advanced HCC, the FOLFOX-HAIC regimen has gained widespread adoption, demonstrating significant efficacy in improving patient survival rates and establishing itself as a clinically recognized safe and effective interventional therapy.[6] However, a considerable proportion of patients experience abdominal pain during or after HAIC procedures.

According to the results of a multivariate linear regression analysis, approximately 64.6% of patients undergoing HAIC for HCC experienced pain of varying intensities, which could lead to extended hospitalization in milder cases or result in treatment discontinuation or refusal of subsequent interventions in severe cases, directly impacting the therapeutic efficacy of HAIC.[15] Theoretically, the etiology of abdominal pain may be Multivariate, involving chemotherapy-induced vasospasm, acute ischemic necrosis of tumor tissue, release of inflammatory mediators, and individual variations in pain sensitivity.[16] Despite the clinical significance of this issue, current domestic and international studies predominantly focus on the therapeutic efficacy of HAIC in HCC, with a notable paucity of systematic observations and research on intra- and post- procedural pain. This gap in the literature underscores a critical oversight in comprehensively evaluating the safety profile of HAIC procedures, highlighting the need for more targeted research in this area to optimize patient outcomes and treatment protocols.

In the current study, acute moderate to severe abdominal pain occurred in 88 patients, representing 36.37% of all patients undergoing HAIC, within the first 24 h after the procedure. The peak incidence of pain was observed between 6 and 12 h post-HAIC. Notably, this incidence rate is lower than those reported in previous domestic studies.[17] Despite administering non-opioid analgesics to over 60% of patients in our cohort, which contributed to an overall reduction in pain incidence, more than 10% of patients continued to experience moderate to severe abdominal pain. Conventional analgesics often prove inadequate in managing HAIC-induced pain, and high-dose opioids carry the risk of severe adverse effects, including respiratory depression. For patients experiencing moderate to severe abdominal pain, intra-arterial lidocaine administration has demonstrated superior efficacy in mitigating the incidence and severity of post-procedural pain, consequently reducing the length of stay at the hospital.[15,18] These findings underscore the importance of tailored pain management strategies in HAIC and highlight the potential of intra-arterial lidocaine as an effective intervention for HAIC-associated pain.

In the present study, ≥60 years of age was identified as a significant risk factor for moderate to severe post-operative pain following HAIC (OR = 1.028, P = 0.031). This association likely stems from age-related physiological decline, including decreased pain thresholds and reduced hepatic enzyme activity. These findings align with recent studies by Yu et al[9] and Lin et al,[10] who reported similar age-related risk patterns in their analyses of HAIC outcomes. The clinical implications of this finding are particularly relevant given the aging demographic of HCC patients.

The age-related challenges can be overcome by implementing age-stratified dosing protocols, conducting comprehensive liver function assessments to optimize drug administration, and enhancing perioperative pain management strategies. These approaches aim to tailor the treatment to the patient's physiological status rather than the chronological age alone. These findings emphasize the importance of age-specific considerations in HAIC treatment planning and pain management protocols. Addressing these factors may help improve treatment tolerability and outcomes in elderly patients undergoing HAIC for HCC.[19,20]

The findings of the current study revealed that a tumor diameter of ≥5 cm and proximity to the liver capsule are significant risk factors for post-HAIC pain in patients with HCC. Larger tumors often indicate a greater tumor burden, which may lead to compression or invasion of the surrounding vasculature and nerves. This pathophysiology can result in uneven distribution of chemotherapeutic agents within the tumor mass, potentially creating localized areas of high drug concentration that could induce vascular irritation and spasm, thereby exacerbating post-procedural pain.[21] Furthermore, larger tumor volumes are associated with extensive necrosis following treatment, leading to the release of inflammatory mediators such as TNF-α and IL-1β, which can intensify the pain response.[22] Notably, tumors located <1 cm from the liver capsule were identified as an independent risk factor for moderate to severe post-HAIC pain, possibly due to the

more pronounced ischemic pain experienced during the treatment of capsule-proximal tumors. The liver capsule is richly innervated, making it particularly sensitive to ischemic insults and inflammatory processes. Our findings align with those of multiple previous studies, which identified capsular proximity as a primary determinant of pain following interventional procedures in the liver.[23,24]

PVTT has been identified as the strongest predictor of post-interventional pain in HCC patients undergoing embolization procedures.[25] This finding is particularly relevant given HCC's high propensity for portal vein invasion. The presence of PVTT can significantly alter hepatic hemodynamics, impeding portal venous blood flow and increasing portal pressure. These changes may precipitate a cascade of physiological events, including gastrointestinal congestion, edema, and, in severe cases, intestinal ischemia, all of which contribute to an elevated risk of abdominal pain. Furthermore, PVTT can disrupt the intrahepatic distribution of chemotherapeutic agents during HAIC, resulting in localized areas of high drug concentration, potentially triggering more intense inflammatory responses.[26] The synergistic effect of altered hepatic blood flow and uneven drug distribution in the presence of PVTT likely underpins the increased incidence and severity of post-procedural pain observed in these patients.

The preparation time and manufacture of oxaliplatin were identified as significant factors influencing the incidence of moderate to severe pain in the present study. This association may be attributed to variations in drug purity and impurity profiles among oxaliplatin products from different manufacturers, potentially affecting the therapeutic efficacy and adverse event profiles.[27] Prolonged preparation times during HAIC procedures may compromise oxaliplatin stability, leading to oxalate precipitation. Notably, oxalate has been implicated in cold-induced hypersensitivity reactions observed exclusively in patients receiving oxaliplatin but not cisplatin. The pain associated with these reactions is thought to result from extracellular calcium ion chelation.[15]

Thus, the implementation of standardized drug preparation and administration protocols, including strict time constraints for oxaliplatin reconstitution and infusion, is warranted. These measures may reduce the likelihood of drug degradation and related complications.[3] These findings underscore the importance of developing individualized post-operative pain management strategies, conducting rigorous evaluations of oxaliplatin manufacturers, and enhancing patient education to improve pain management awareness and outcomes.

However, several limitations of this study warrant consideration. First, as a single-center study, it may be subject to selection bias. Second, the relatively small sample size limits the generalizability of our findings, necessitating further exploration in larger cohorts. Lastly, the model has not undergone external validation, and its performance in diverse populations remains to be evaluated. These limitations underscore the need for future prospective, multi-center studies to further explore and optimize the model, thereby enhancing its predictive efficacy and clinical utility. Additionally, research into novel pain management strategies, particularly for high-risk patients, could build upon our findings. The role of different chemotherapy preparation protocols and their impact on pain outcomes represents another important avenue for investigation.

Conclusion

In conclusion, this study provides preliminary evidence for a risk prediction model of acute moderate to severe abdominal pain in patients following HAIC, offering valuable insights for clinical decision-making. Our findings suggest that age, tumor diameter, distance from the liver capsule, presence of PVTT, and the preparation time and manufacture of oxaliplatin are critical for predicting the risk of acute moderate to severe abdominal pain after HAIC. This model elucidates the complex pathophysiological mechanisms underlying post-HAIC pain and establishes a scientific foundation for developing individualized pain management strategies. Clinicians may utilize these factors to conduct preoperative risk assessments and implement preventive medication and timely symptomatic treatment for high-risk patients. These approaches have the potential to significantly enhance the quality of life for post-HAIC patients, reduce the hospital stays, and improve the overall treatment experiences.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author (Jin-peng Li).

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality Worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a Phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25–34. doi:10.1016/S1470-2045(08)70285-7
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69 (1):182–236. doi:10.1016/j.jhep.2018.03.019
4. Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines insights: hepatobiliary cancers, version 2.2019. *J Natl Compr Canc Netw*. 2019;17 (4):302–310. doi:10.6004/jnccn.2019.0019
5. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol*. 1954;30(5):969–977.
6. Qin S, Zhang X, Guo W, et al. Prognostic nomogram for advanced hepatocellular carcinoma treated with FOLFOX 4. *Asian Pac J Cancer Prev*. 2017;18(5):1225–1232. doi:10.22034/APJCP.2017.18.5.1225
7. Lyu N, Lin Y, Kong Y, et al. FOXAI: a Phase II trial evaluating the efficacy and safety of hepatic arterial infusion of oxaliplatin plus fluorouracil/ leucovorin for advanced hepatocellular carcinoma. *Gut*. 2018;67(2):395–396. doi:10.1136/gutjnl-2017-314138
8. Li QJ, He MK, Chen HW, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus transarterial chemoembolization for large hepatocellular carcinoma: a randomized phase III trial. *J Clin Oncol*. 2022;40(2):150–160. doi:10.1200/JCO.21.00608
9. Yu X, Cui R, Jiang Y, et al. Efficacy and safety of atezolizumab combined with bevacizumab, arterial chemoembolization, and hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma: a meta-analysis. *Int J Clin Exp Pathol*. 2024;17(12):444–457. doi:10.62347/ MBQJ8679
10. Lin ZP, Hu XL, Chen D, et al. Efficacy and safety of targeted therapy plus immunotherapy combined with hepatic artery infusion chemotherapy (FOLFOX) for unresectable hepatocarcinoma. *World J Gastroenterol*. 2024;30(17):2321–2331. doi:10.3748/wjg.v30.i17.2321
11. Janczewski LM, Joung RH, Borhani AA, et al. Safety and feasibility of establishing an adjuvant hepatic artery infusion program. *HPB*. 2024;26 (5):656–663. doi:10.1016/j.hpb.2023.12.006
12. Medical Administration Bureau of National Health and Family Planning Commission. Guidelines for diagnosis and treatment of primary liver cancer (2017 edition). *Chin J Dig Surg*. 2017;16(7):635–647.
13. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res*. 2011;63(Suppl 11): S240–S252. doi:10.1002/acr.20543
14. Lyu N, Wang X, Li JB, et al. Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: a biomolecular exploratory, randomized, phase III trial (FOHAIC-1). *J Clin Oncol*. 2022;40(5):468–480. doi:10.1200/JCO.21.01963
15. Wu Z, Guo W, Chen S, et al. Determinants of pain in advanced HCC patients recieving hepatic artery infusion chemotherapy. *Invest New Drugs*. 2021;39(2):394–399. doi:10.1007/s10637-020-01009-x
16. Lv N, Kong Y, Mu L, et al. Effect of perioperative parecoxib sodium on postoperative pain control for transcatheter arterial chemoembolization for inoperable hepatocellular carcinoma: a prospective randomized trial. *Eur Radiol*. 2016;26(10):3492–3499. doi:10.1007/s00330-016-4207-8
17. Luo J, Shao GL, Zheng JP, et al. Incidence pattern and influencing factors of abdominal pain after transcatheter arterial chemoembolization for primary liver cancer. *J Interv Radiol*. 2017;26(7):613–617.
18. Hartnell GG, Gates J, Stuart K, et al. Hepatic chemoembolization: effect of intraarterial lidocaine on pain and postprocedure recovery. *Cardiovasc Intervent Radiol*. 1999;22(4):293–297. doi:10.1007/s002709900391
19. Zheng MD, Wei JW, Ju SW, et al. Analysis of influencing factors of residual pain after PVP for osteoporotic vertebral compression fracture. *Chin J Bone Jt Inj*. 2020;35(1):46–48.
20. Urban D, Cherny N, Catane R. The management of cancer pain in the elderly. *Crit Rev Oncol Hematol*. 2010;73(2):176–183. doi:10.1016/j. critrevonc.2009.03.008
21. Khalaf MH, Sundaram V, AbdelRazek Mohammed MA, et al. A predictive model for postembolization syndrome after transarterial hepatic chemoembolization of hepatocellular carcinoma. *Radiology*. 2019;290(1):254–261. doi:10.1148/radiol.2018180257
22. Pachev A, Raynaud L, Paulatto L, et al. Predictive factors of severe abdominal pain during and after transarterial chemoembolization for hepatocellular carcinoma. *Eur Radiol*. 2021;31(5):3267–3275. doi:10.1007/s00330-020-07404-5
23. Yang Y, Chen S, Yan Z, et al. Construction and validation of prediction model of severe abdominal pain post-transarterial chemoembolization in patients with HBV-associated primary liver cancer. *Comput Math Methods Med*. 2022;2022:5203166. doi:10.1155/2022/5203166
24. Park SJ, Lee DH, Han JK. Reducing pain by artificial ascites infusion during radiofrequency ablation for subcapsular hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. 2021;44(4):565–573. doi:10.1007/s00270-020-02723-y
25. Li T, Liu C, He JT, et al. Portal stent with endovascular brachytherapy improves the efficacy of TACE for hepatocellular carcinoma with main portal vein tumor thrombus. *Hepatobiliary Pancreat Dis Int*. 2020;19(2):187–190. doi:10.1016/j.hbpd.2019.10.005

26. Yu JI, Park HC, Jung SH, et al. Combination treatment with transarterial chemoembolization, radiotherapy, and hyperthermia (CERT) for hepatocellular carcinoma with portal vein tumor thrombosis: final results of a prospective phase II trial. *Oncotarget*. 2017;8(32):52651–52664. doi:10.18632/oncotarget.17072
27. Sałat K. Chemotherapy-induced peripheral neuropathy-part 2: focus on the prevention of oxaliplatin-induced neurotoxicity. *Pharmacol Rep*. 2020;72(3):508–527. doi:10.1007/s43440-020-00106-1

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