Frailty as a Predictor of Complications and Transplant-Free Survival after Transarterial Chemoembolization of Hepatocellular Carcinoma

Rana Rabei[1] Parmede Vakil[1] Bradley King[1] R. Peter Lokken[1] Michael Heller[1] Nicholas Fidelman[1] Maureen Kohi[2]

[1] Department of Interventional Radiology, University of California, San Francisco, San Francisco, California, United States
[2] Department of Radiology, University of North Carolina, Chapel Hill, North Carolina, United States

Address for correspondence Rana Rabei, MD, Department of Interventional Radiology, University of California, San Francisco, San Francisco, CA 94143, United States (e-mail: rana.rabei@gmail.com).

J Clin Interv Radiol ISVIR 2023;7:27–33.

Abstract

Purpose To determine the association between frailty, 30-day complications, rehospitalization, and transplant-free survival (TFS) following conventional and drug-eluting bead transarterial chemoembolization.

Materials and Methods A retrospective analysis was performed on a cohort of 125 patients with treatment-naïve hepatocellular carcinoma who underwent conventional or drug-eluting beads chemoembolization at our institution between 2014 and 2015. Liver function parameters, Barcelona clinic liver cancer tumor stage, and all components of the five-item modified frailty index (mFI-5) were used to determine the patient's frailty status. Key end points included severe (grade 3 or above) adverse events of chemoembolization, 30-day rehospitalization rates, and TFS. Logistic regression analysis was performed on conventional predictors of postoperative complications after chemoembolization. Median survival was estimated and compared using the Kaplan–Meier's estimator and log-rank test.

Results Among 125 patients who underwent first-time chemoembolization, higher frailty score was an independent predictor of both 30-day hospital readmission and severe liver toxicity ($p = 0.01$ and $p = 0.03$, respectively) on multivariate logistic regression analysis. Each point increase in mFI-5 conferred a threefold or twofold increase in the risk of experiencing 30-day rehospitalization or postoperative severe adverse events, respectively. At the data censor date, patients with mFI-5 score ≥ 2 had decreased overall TFS (28.1 vs. 39.8 months, $p = 0.03$).

Conclusion Increasing frailty as determined by mFI-5 is an independent predictor of 30-day complications and lower TFS following chemoembolization.

Keywords
- oncology
- frailty
- TACE

article published online
May 17, 2022

DOI https://doi.org/10.1055/s-0042-1745775.
ISSN 2457-0214.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Two-thirds of new HCC diagnoses are made at an advanced stage, precluding these patients from curative options other than liver transplantation.[1–3] Thus, locoregional intra-arterial therapies including transarterial chemoembolization (TACE) and transarterial radioembolization yttrium-90 are used to bridge or downstage these patients to liver transplant or as a means of palliation to delay tumor progression.

Currently, TACE is the most common treatment modality employed for HCC for downstaging, bridging to liver transplant, and palliation in patients with unresectable HCC.[4–7] Given the heterogeneity of the TACE population, current understanding of prognostic factors for procedural morbidity and mortality following TACE remains limited. Advanced tumor burden (Barcelona clinic liver cancer [BCLC] classes C and D, elevated alpha-fetoprotein), poor liver synthetic function (Child–Pugh class C, albumin-bilirubin grade 3), prior transjugular intrahepatic portosystemic shunt placement, or hepatofugal portal venous flow has previously been associated with higher risk of acute hepatic decompensation and mortality after TACE. However, granularity on patient-specific factors is currently lacking.[8–11] Prior studies have not demonstrated a significant association between Eastern Cooperative Oncology Group performance status and outcomes after TACE, but these findings may be confounded by the bias and interobserver variability intrinsic to this scoring system.[12]

Frailty is defined as the state of increased vulnerability to stress due to decreased physiologic reserve and represents an emerging concept in the surgical literature due to its association with postoperative complications and mortality. Frailty can be characterized by physical phenotype (loss of grip strength, walking speed, etc.) or age-related accumulation of deficits (decreased functional status, comorbidities, etc.).[13] The Canada Study of Health and Aging (CSHA), a large, 5-year prospective cohort study initially identified 70 factors which capture frailty as well as predict morbidity and mortality in the elderly population.[14] The five-item modified frailty index (mFI-5) was subsequently developed based on CSHA patient characteristics available through the National Surgical Quality Improvement Program (NSQIP) database. This scoring system demonstrated predictive value for postoperative complications, prolonged hospitalization, discharge to a long-term care facility, and mortality in elderly patients across various surgical subspecialties.[15–17]

To date, the mFI-5 has not been studied in patients undergoing TACE, and its utility in predicting postprocedure complications and mortality remains unknown. The purpose of this study was to determine if the mFI-5 would be predictive of 30-day complications and transplant-free survival (TFS) among patients with HCC receiving TACE.

Materials and Methods

Experimental Design

This single-center, retrospective cohort study is Health Insurance Portability and Accountability Act compliant and was approved by the Institutional Review Board at our institution. A waiver of informed consent was provided for retrospective review of medical records.

From January 1, 2014, to December 31, 2015, a total of 210 patients with previously untreated HCC diagnosed by American Association for the Study of Liver Disease criteria or percutaneous biopsy underwent 280 TACE procedures at our institution. Patients with a history of liver-directed transarterial or ablative therapy, surgical resection, radiation, or systemic therapy for HCC were excluded. In addition, patients who underwent an additional liver-directed intervention 30 days after the TACE procedure were excluded.

Using our institution's electronic medical record, variables for calculation of model for end-stage liver disease (MELD), Child–Pugh (CP) score, BCLC staging, tumor characteristics, TNM staging, and all components of the mFI-5 (►**Table 1**) at the time of the procedure were collected. Each patient was assigned an mFI-5 score of 0 to 5. Clinical and laboratory severe adverse events (SAEs) that occurred within 30 days of TACE were classified according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0, and survival was recorded for 5 years through December 31, 2019. The primary outcomes were severe liver toxicity (grade 3 or above), hospital readmission at 30 days, and TFS.

Procedural Details

Recommendations for treatment with TACE were made by a multidisciplinary team consisting of hepatologists, medical oncologists, radiation oncologists, transplant surgeons, and interventional radiologists after consideration of tumor burden, tumor location, performance status, and liver transplantation waiting status. All procedures were performed at a transplant center by fellowship-trained interventional radiologists with 2 to 25 years of experience. Depending on lesion size, number, and distribution, up to two Couinaud liver segments were targeted during TACE.

Table 1 Components of mFI-5 score

Impaired functional status—partially or totally dependent	1 point
History of COPD or current pneumonia	1 point
Congestive heart failure present in past 30 d	1 point
Hypertension requiring medication	1 point
Diabetes mellitus	1 point
Total	5 points

Abbreviations: COPD, chronic obstructive pulmonary disease; mFI-5, five-item modified frailty index.

Embolization was performed until at least five-heart beat stasis was achieved. Operator preference and drug availability determined the use of conventional TACE (cTACE) or TACE with drug-eluting bead microspheres (DEB-TACE). cTACE was performed using a solution of 25 mg doxorubicin dissolved in 5 mL iohexol (Omnipaque 300; GE Healthcare, Waukesha, Wisconsin, United States) that was subsequently emulsified in a 1:2 volume ratio with 10 mL ethiodized oil (Lipiodol; Guerbet LLC, Bloomington, Indiana, United States). Embolization was performed with gelatin sponge slurry. Drug-eluting microspheres (100–300 and/or 300–500 µm LC Bead; Boston Scientific, Natick, Massachusetts, United States) were loaded with 75 mg doxorubicin per 2 mL vial of microspheres per manufacturer instructions for a maximum delivery dose of 150 mg of doxorubicin. The microspheres were reconstituted in iohexol prior to intra-arterial delivery.

Statistical Analysis

Normally distributed continuous variables were reported as mean ± standard deviation and compared using Student's *t*-test. Nonnormally distributed continuous variables were presented as median and interquartile range and compared using the chi-square test. Univariate logistic regression was performed on conventional predictors of postoperative complications after chemoembolization. Covariates were then incorporated into multivariate models based on a statistically significant univariate relationship. Kaplan–Meier's curves were constructed and compared with the log-rank test followed by the Cox proportional regression model with censoring for transplantation. Significance was defined at the $p < 0.05$ level. All statistical analysis was performed using MATLAB v2015b (MathWorks, Nattick, Massachusetts, United States) and R Project v3.6.1 (R Foundation for Statistical Computing, 2017, Vienna, Austria).

Table 2 Characteristics of patient cohort

Patient characteristic	Values $N = 125$
Age (y)	63 ± 9.5
Male gender	94 (75.2%)
Risk factors	
Hepatitis C	84 (67.2%)
Hepatitis B	16 (12.8%)
Ethanol	33 (26.4%)
Nonalcoholic steatohepatitis	12 (9.6%)
Primary biliary cholangitis	1 (0.8%)
BCLC stage	
A	13 (10.4%)
B	76 (60.8%)
C	32 (25.6%)
D	4 (3.2%)
Child–Pugh	
A	68
B	25
C	9
Transplant eligible	26
DEB-TACE	71
cTACE	54
Single nodule	83
Multiple nodules	111
Maximum tumor size (cm)	3.1 ± 1.8

Abbreviations: BCLC, Barcelona clinic liver cancer; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.

Results

Patient Characteristics

A total of 125 patients (75% men, age 63 ± 9.5 years) with treatment naïve HCC were included in the study. Demographic and clinical features are shown in ►**Table 2**. Chronic hepatitis C (84 patients) and alcohol-related cirrhosis (33 patients) were the most common risk factors for HCC in our cohort. A majority of patients were BCLC stage B (61%, 76), while only 13, 32, and 4 patients were BCLC stages A, C, and D, respectively. Approximately 54% (68) of patients were CP class A, while only 25 and 9 patients were CP classes B and C, respectively. Twenty-six (21%) patients were eligible for liver transplant.

Clinical Complications and Laboratory Toxicity Postchemoembolization

In total, patients in our cohort experienced 13 grade 3 or above toxicity events, and 9 patients were rehospitalized during the 30-day postprocedural period. Univariate logistic regression analyses between various demographic markers and key 30-day complication end points are summarized in ►**Table 3**. MELD and mFI-5 were significantly associated with rehospitalization ($p = 0.04$ and $p = 0.008$, respectively). In addition, mFI-5 ($p = 0.048$) and BCLC stage ($p = 0.04$) were associated with post-TACE SAE.

On multivariate analysis, MELD score and mFI-5 each independently predicted 30-day hospital readmission ($p = 0.03$ and $p = 0.01$, respectively). Each additional point increase in mFI-5 conferred threefold greater odds of rehospitalization within 30 days. Pneumonia (three of nine cases) and urinary retention/urinary tract infection (three of nine cases) were the leading causes of rehospitalization after TACE. Preprocedural mFI-5 and BCLC stage were also independent predictors of severe post-TACE SAE at 30 days ($p = 0.03$ and $p = 0.03$). A twofold increase in the odds of liver SAE was observed with incremental increases in mFI-5 score. This is further illustrated through boxplots of mFI-5 scores stratified by 30-day rehospitalization and severe liver toxicity (►**Fig. 1**) where mean mFI-5 scores were significantly greater in rehospitalized patients (Student's *t*-test, $p = 0.003$) and those with severe liver toxicity (Student's *t*-test, $p = 0.04$).

Table 3 Relationship between patient characteristics and 30-day rehospitalization and liver toxicity

Univariate and multivariate logistic regression of demographic markers against outcomes						
	Rehospitalization		Toxicity		Mortality 1 y post-TACE	
	OR (95% CI)	*p*–Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Univariate analysis						
Sex	0.27 (0.07, 1.06)	0.060	0.82 (0.24, 2.87)	0.76	0.38 (0.13, 1.1)	0.070
Age	1.07 (0.99, 1.15)	0.070	1.06 (0.99, 1.13)	0.08	0.97 (0.92, 1.02)	0.200
BCLC class	1.7 (0.64, 4.52)	0.290	**0.34 (0.13, 0.93)**	**0.04**	2.57 (1.19, 5.56)	0.020
CP class	2.01 (0.78, 5.2)	0.150	1.21 (0.47, 3.14)	0.69	6.95 (2.58, 18.67)	0.000
MELD	**1.21 (1.01, 1.45)**	**0.040**	0.97 (0.8, 1.19)	0.8	1.57 (1.26, 1.96)	0.000
Net frailty score	**2.78 (1.31, 5.89)**	**0.010**	**1.81 (1.01, 3.26)**	**0.0475**	1.22 (0.7, 2.1)	0.480
Multivariate analyses						
Model 1						
Net frailty	3.09 (1.36, 6.99)	0.010				
BCLC	1.23 (1.02, 1.49)	0.030				
Model 2			2.05 (1.06, 3.95)	0.030		
Net frailty			0.3 (0.1, 0.87)	0.030		
BCLC						

Abbreviations: BCLC, Barcelona clinic liver cancer; CI, confidence interval; CP, Child–Pugh; MELD, model for end-stage liver disease; OR, odds ratio; TACE, transarterial chemoembolization.
Note: Bold indicates the statistically significant values.

Survival

At the time of data censor date, 49% (61) of the patients had died with 33% (20) of the deaths occurring within 1 year of TACE. Median overall survival was 48.9 months with median follow-up time (reverse Kaplan–Meier) of 57.3 months. After censoring for transplantation, survival was 33.7 months (►**Fig. 2**) with median follow-up time of 49.2 months. In stratified Kaplan–Meier analysis of TFS, patients with mFI-5 score ≥ 2 demonstrated decreased survival at the time of data censor date (median survival time 28.1 vs. 39.8 months, log-rank $p = 0.03$) and at 4 years following TACE (log-rank $p = 0.05$) but not at 1 year ($p = 0.09$) (►**Fig. 3**).

►**Table 3** summarizes findings of Cox proportional hazards regression analysis. On univariate analysis, there was higher hazard of death after TACE for patients with higher BCLC stage, CP class, and MELD score at 1 year, 4 years, and at the time of study closure. Patients with a mFI-5 score of 2 or more demonstrated significantly lower TFS at 4 years post-TACE (hazard ratio [HR]: 1.7, confidence interval [CI]: 1.0–2.9, $p = 0.05$) and at study closure (HR: 1.7, CI: 1.04–2.9, $p = 0.04$). There was increased hazard of death at 1 through 3 years following TACE, though this was not statistically significant: HR of 2.1 at 1 year ($p = 0.1$), HR of 1.7 at 2 years ($p = 0.1$) and HR of 1.6 at 3 years ($p = 0.09$). Multivariate Cox

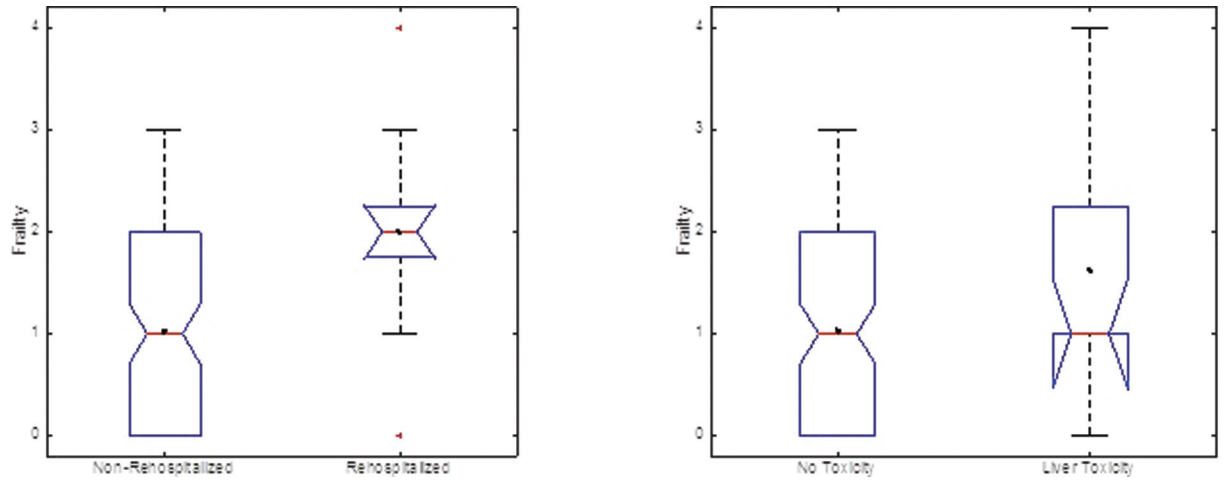

Fig. 1 A 30-day complications after chemoembolization stratified by frailty. Higher mean (*) preoperative frailty was present in patients who experienced 30-day rehospitalization ($p = 0.003$) and patients with grade 3 liver toxicity ($p = 0.04$). Note: "*" is the black dot that indicates the mean in each of the plots (overlies the red line).

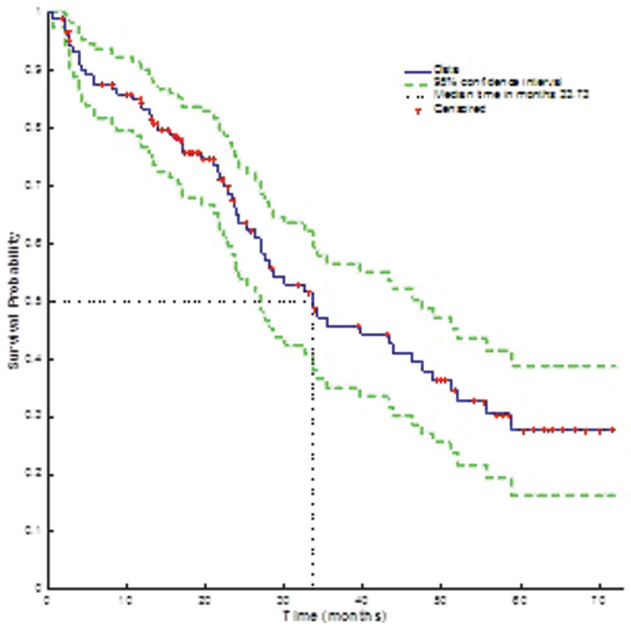

Fig. 2 Kaplan–Meier's plot of overall transplant-free survival in our study population demonstrating a median survival of 33.7 months.

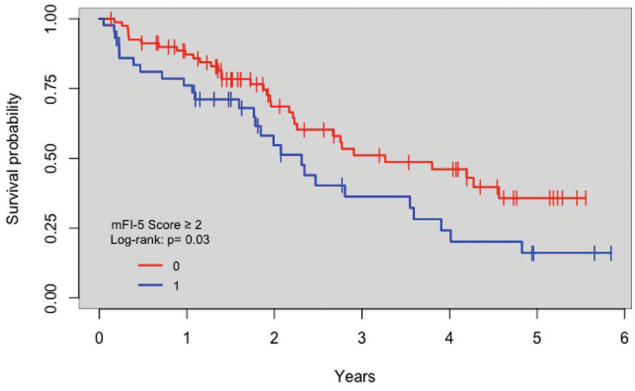

Fig. 3 Transplant-free survival stratified by frailty. Patients with mFI-5 score ≥ 2 had median survival of 28.1 versus 39.8 months for patients with mFI-5 < 2 ($p = 0.03$, log-rank test). mFI-5, five-item modified frailty index.

regression analysis at study closure considered mFI-5 ≥ 2, BCLC stage, tumor stage, and number of nodules with only mFI-5 ≥ 2 as a statistically significant predictor of lower TFS (HR: 1.8, CI: 1.1–3.1, $p = 0.02$). Of note, frail patients were less likely to undergo liver transplantation (odds ratio = 0.5, CI: 0.3–0.8, $p = 0.01$), and patients who underwent transplant had lower frailty scores (mean mFI-5 score = 0.6 vs. 1.2, $p = 0.008$).

Discussion

Frailty as determined by mFI-5 score of 2 or more independently predicted higher risk of post-TACE complications and lower TFS after chemoembolization. Within the 30-day postprocedural period, frail patients were found to have a significantly higher likelihood of hepatic decompensation and greater risk of rehospitalization for treatment of urinary retention as well as pulmonary and urinary tract infections.

While the predictive value of frailty using the mFI-5 index in TACE patients has not been previously studied, the implications of frailty on preoperative risk assessment have been the subject of extensive research across surgical specialties. Large-scale retrospective reviews applying the mFI-5—and its earlier version, the mFI-11—to data from the NSQIP database have shown that frailty is predictive of poor surgical outcomes, higher mortality, increased length of hospitalization, and readmission. These associations are present in a variety of surgical settings, including vascular surgery and surgical oncology, that have similar patient populations to those in interventional radiology.[18–21]

Although TACE is a minimally invasive procedure, the periprocedural requirement of presedation fasting, sedation, and immobilization during and for up to 6 hours following the procedure, as well as the postprocedural recovery can produce a significant physiologic strain on a frail individual. It has been proposed that the accumulation of multiorgan deficits and sarcopenia that characterizes frailty has an impact on pharmacokinetics of drug metabolism that increases risk of oversedation.[22–24] Postoperatively, reduced respiratory muscle strength has been associated with higher risk of pulmonary complications, which account for 40% of deaths in the geriatric population.[25] Frail patients are more likely to have preexisting cognitive impairment, which places them at a higher risk of postprocedure delirium.[23] Additionally, they are more likely to experience longer periods of diminished mobility after procedures, leading to further deconditioning. Age is a known risk factor for urinary retention and urinary tract infections, which has a higher risk of evolving into sepsis in frail patients due to a weakened immune system.[26,27]

In cirrhotic patients, in particular, a performance-based frailty index based on grip strength, chair stands, and balance has demonstrated higher predictive value for transplant waitlist mortality than MELD-Na alone.[28] This has led our institution, among many others, to incorporate frailty assessments into the transplant work-up process to identify patients at higher risk of decompensation.[28–30] In our cohort, patients with higher mFI-5 trended toward incrementally greater hazard of death during the first 3 years following TACE and demonstrated significantly lower TFS 4 and 5 years postprocedurally. This finding, along with the previously established association between frailty and higher transplant-waitlist mortality, supports the notion that frail patients may benefit from decreasing their waitlist time by accepting higher risk donor livers and pursing living donor transplants. However, given the higher incidence of postprocedural complications and rehospitalization after chemoembolization, aggressive TACE treatment with the goal of downstaging may be inappropriate as a means to achieve this goal in frail patients. Future research could evaluate whether technical factors such as decreasing dose and treatment area can improve outcomes in these patients.

Frailty is a reversible phenomenon that can be improved with nutritional support and physical therapy.[28,31] Therefore, incorporating a preoperative frailty assessment in the interventional radiology clinic and providing targeted support and counseling to frail patients has the potential to improve both short-term and long-term outcomes after TACE.

This study has several limitations including utilization of data from a single institution, a relatively small sample size, and retrospective study design. In this study, we did not identify a significant association between frailty and mortality over 3 years immediately following TACE. Given that other studies have seen higher transplant waitlist mortality in frail patients, our results may reflect a type II error from a small sample size. Alternatively, severity of hepatic disease may be the primary driver of short-term mortality after TACE with frailty becoming an increasingly important predictor of long-term survival. In addition, nonfrail patients in this study had a twofold greater likelihood of receiving a transplant, highlighting the inherent limitations in using TFS as an end point in studying the impact of frailty in an HCC population of whom a significant subgroup will undergo transplant. Future prospective multicenter studies can anticipate these effects, and with appropriate control, elucidate the questions and hypotheses generated by this retrospective study.

Conclusion

Frailty as determined by mFI-5 score of ≥ 2 was found to be an independent predictor of 30-day hospital readmission, severe liver toxicity, and TFS after TACE in treatment-naïve patients. Preprocedural frailty evaluation is a promising risk stratification tool for TACE candidates that should be incorporated into patient counseling and used to inform targeted periprocedural nutritional and functional interventions for high-risk patients.

Note

For this type of study, formal consent is not required. This single-center, retrospective cohort study is Health Insurance Portability and Accountability Act compliant and was approved by the Institutional Review Board at our institution.

Funding

None.

Ethical approval

The article was exempted from an ethical committee approval.

Conflict of Interest

R.P.L. has received consulting fees from Neptune Medical in Burlingame, California, United States outside the presented work and N.F. is the recipient of research grants from Sirtex Medical, Merck, and Boston Scientific.

References

1 Dohmen K, Shirahama M, Shigematsu H, Irie K, Ishibashi H. Optimal treatment strategy for elderly patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2004;19(08):859–865
2 El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. Hepatol Res 2007;37(Suppl 2):S88–S94
3 Padhya KT, Marrero JA, Singal AG. Recent advances in the treatment of hepatocellular carcinoma. Curr Opin Gastroenterol 2013; 29(03):285–292
4 Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant 2010;10(4 Pt 2):1003–1019
5 Bruix J, Sherman MAmerican Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53(03):1020–1022
6 Marrero JA. Multidisciplinary management of hepatocellular carcinoma: where are we today? Semin Liver Dis 2013;33(1, suppl 1):S3–S10
7 Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35(03):519–524
8 Barman PM, Sharma P, Krishnamurthy V, et al. Predictors of mortality in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. Dig Dis Sci 2014;59(11): 2821–2825
9 Wang Y, Chen Y, Ge N, et al. Prognostic significance of alpha-fetoprotein status in the outcome of hepatocellular carcinoma after treatment of transarterial chemoembolization. Ann Surg Oncol 2012;19(11):3540–3546
10 Hansmann J, Evers MJ, Bui JT, et al. Albumin-bilirubin and platelet-albumin-bilirubin grades accurately predict overall survival in high-risk patients undergoing conventional transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol 2017;28(09):1224–1231.e2
11 Lokken RP, Kerlan RK Jr, Chung YC, et al. Hepatic toxicity after selective chemoembolization is associated with decreased survival among patients with hepatocellular carcinoma. AJR Am J Roentgenol 2021;216(05):1283–1290
12 Ray CE Jr, Brown AC, Green TJ, et al. Survival outcomes in patients with advanced hepatocellular carcinoma treated with drug-eluting bead chemoembolization. AJR Am J Roentgenol 2015;204(02): 440–447
13 Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. Age Ageing 2012;41(02):142–147
14 Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(05): 489–495
15 Subramaniam S, Aalberg JJ, Soriano RP, Divino CM. New 5-factor modified frailty index using American College of Surgeons NSQIP Data. J Am Coll Surg 2018;226(02):173–181.e8
16 Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg 2010;210(06): 901–908
17 Shinall MC Jr, Arya S, Youk A, et al. Association of preoperative patient frailty and operative stress with postoperative mortality. JAMA Surg 2020;155(01):e194620
18 Arya S, Kim SI, Duwayri Y, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. J Vasc Surg 2015;61(02):324–331
19 Adams P, Ghanem T, Stachler R, Hall F, Velanovich V, Rubinfeld I. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery. JAMA Otolaryngol Head Neck Surg 2013;139 (08):783–789
20 Wahl TS, Graham LA, Hawn MT, et al. Association of the modified frailty index with 30-day surgical readmission. JAMA Surg 2017; 152(08):749–757

21 Wang J, Zou Y, Zhao J, et al. The impact of frailty on outcomes of elderly patients after major vascular surgery: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2018;56(04):591–602
22 Lin HS, McBride RL, Hubbard RE. Frailty and anesthesia - risks during and post-surgery. Local Reg Anesth 2018;11:61–73
23 McIsaac DI, MacDonald DB, Aucoin SD. Frailty for perioperative clinicians: a narrative review. Anesth Analg 2020;130(06):1450–1460
24 Franken LG, de Winter BC, van Esch HJ, et al. Pharmacokinetic considerations and recommendations in palliative care, with focus on morphine, midazolam and haloperidol. Expert Opin Drug Metab Toxicol 2016;12(06):669–680
25 Fernandez-Bustamante A, Sprung J, Cartin-Ceba R, Weingarten TN, Warner DO. The aging respiratory system: strategies to minimize postoperative pulmonary complications. In: Geriatric Anesthesiology. Springer, Cham; 2018:179–196
26 Amrock LG, Deiner S. Perioperative frailty. Int Anesthesiol Clin 2014;52(04):26–41
27 Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. Age Ageing 2012;41(02):142–147
28 Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant 2014;14(08):1870–1879
29 Lai JC, Dodge JL, Kappus MR, et al; Multi-Center Functional Assessment in Liver Transplantation (FrAILT) Study. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. J Hepatol 2020;73(03):575–581
30 Lai JC, Covinsky KE, Dodge JL, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66(02):564–574
31 Buchard B, Boirie Y, Cassagnes L, Lamblin G, Coilly A, Abergel A. Assessment of malnutrition, sarcopenia and frailty in patients with cirrhosis: which tools should we use in clinical practice? Nutrients 2020;12(01):186

