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ORIGINAL RESEARCH

Effectiveness of Minimally Invasive Hepatectomy in Patients with Early or Intermediate-Stage Hepatocellular Carcinoma: A Multi-Institutional Cohort Study in an Asian Population

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Purpose: Minimally invasive hepatectomy (MIH) has been increasingly applied for patients with hepatocellular carcinoma (HCC). However, the effectiveness of MIH has yet to be well established.

Patients and Methods: This retrospective cohort study included patients aged 20 years and older, newly receiving MIH for HCC with Barcelona Clinic Liver Cancer (BCLC) classification stage 0, A or B from 2010 to 2019. Two 1:1 propensity score-matched cohorts of those receiving open hepatectomy (OH) and those receiving radiofrequency ablation (RFA) were selected as comparison groups. As a control analysis, we compared patients receiving OH with those receiving RFA under the hypothesis that the OH group had better survival outcomes than the RFA group.

Results: We included a total of 555 matched patients receiving MIH or OH, and 382 matched patients receiving MIH or RFA. Compared to the OH group, MIH group was associated with better overall survival (OS) (Hazard ratios (HR): 0.62; 95% CI: 0.43–0.88) and similar PFS (HR: 0.92; 0.74–1.16). Compared to the RFA group, we found the MIH group was associated with better OS (0.46; 0.32–0.67) and better PFS (0.48; 0.38–0.61). We found consistent results from a series of subgroup analyses (eg, age groups, BCLC stages and hospital levels) and sensitivity analyses (eg, study period restricted to the most recent 5 years (2015–2019)). The control analysis (OH group vs RFA group) confirmed the robustness of main analyses.

Conclusion: Our study suggested that MIH had better survival outcomes for patients with early or resectable intermediate-stage HCC, compared to RFA or OH.

Keywords: hepatocellular carcinoma, minimally invasive hepatectomy, open hepatectomy, radiofrequency ablation, long-term survival

Introduction

Hepatocellular carcinoma (HCC) is one of the major primary liver cancers worldwide and the fourth most common cause of cancer-related death in many parts of the world.[1] Furthermore, it accounts for over 70% of primary liver malignancies and has shown an increase in incidence over the past decades.[2] By understanding the tumor microenvironment and the

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complexity of the immune system in HCC, treatments such as anti-programmed cell death 1 immunotherapy and natural killer cell therapy have gradually emerged as important options in HCC management.[3,4] Nonetheless, curative-intent treatments, including surgical resection and radiofrequency ablation (RFA), remain the cornerstone for the early-stage HCC population. According to the Barcelona Clinic Liver Cancer (BCLC) consensus, the curative treatment for patients with early-stage HCC includes surgical resection (minimally invasive hepatectomy (MIH), open hepatectomy (OH)) and RFA. Specifically, MIH has been widely applied in liver resection since it is associated with less blood loss and can preserve patient immunity. The indication for MIH has evolved from minor hepatectomy in the Louisville consensus of 2008 to major resection in the Morioka consensus of 2015.[5,6]

Previous studies have proven MIH to be a safe procedure with lower postoperative morbidity and mortality and shorter length of hospital stay,[7,8] but it has hitherto lacked a proper assessment of survival outcomes, including overall survival (OS) and progression-free survival (PFS). Some observational studies compare the efficacy between MIH and OH in patients with HCC.[9–11] However, possibly due to limited sample sizes in the single-center analyses, we found large random errors and conflicting results regarding survival outcomes in these studies. Other studies evaluate the survival outcomes of MIH versus RFA,[12–14] but reach no definitive conclusion because of clinical and statistical heterogeneity among studies. Therefore, we conducted a retrospective cohort study by analyzing a large, multi-institutional electronic health records (EHR) database with records of approximately 1.3 million individuals to evaluate the effectiveness of MIH as regards survival outcomes for patients with early and resectable intermediate-stage HCC. To minimize potential selection bias, we selected two comparison groups, consisting of patients receiving OH or RFA with similar probabilities of being assigned to a specific procedure group (ie, propensity score). In the propensity score models we considered a large number of covariates including patients' health-risk behaviors (eg, smoking, alcohol- and betel nut consumption), all medical records and laboratory data.

Materials and Methods

Data Sources

This study analyzed the Chang Gung Research Database (CGRD), the EHR database of the largest multi-institutional healthcare system (ie, Chang Gung Medical Foundation, CGMF) in Taiwan.[15] The CGMF includes seven medical institutions, covering 1.3 million individuals (approximately 6% of Taiwan's entire population of 23 million). The CGRD contains inpatient and outpatient healthcare records, including procedures, laboratory results and pathological- and pharmacy records. Moreover, we linked the EHR to the Taiwan Cancer Registry and Taiwan Cause of Death database to obtain details of status and progression of cancer and death information.[16] The details of data structures[15] and disease coding validity[17–22] in the CGRD have been described in previous literature. This study was approved by the Institutional Review Board of CGMF (ID: 202001650B0). The study complies with the Declaration of Helsinki, and the data accessed complied with relevant data protection and privacy regulations. Thus, the need for informed consent was waived.

Study Design and Cohort

This retrospective cohort study included patients aged 20 years and older, newly receiving MIH for early or resectable intermediate-stage HCC from 2010 to 2019. HCC diagnosis was identified by the International Classification of Disease 9th Revision Clinical Modification (ICD-9-CM) codes 155.0 and 155.2, or by the International Classification of Disease 10th Revision Clinical Modification (ICD-10-CM) codes C22.0, C22.2, C22.3, C22.4, C22.8 and C22.9. We defined early or resectable intermediate-stage HCC as BCLC stage 0, A and B. We defined the index date as the date of first procedure. We excluded patients with no record in the CGRD before or after the index date in order to ensure sufficient data to evaluate patients' baseline and follow-up information. We excluded patients without BCLC staging in the registry data. To minimize potential selection bias, we selected patients newly receiving OH or RFA as two comparison groups, using identical selection criteria. The flowchart for study cohort assembly is presented in Figure S1.

Study Endpoints and Follow-up

Study outcomes were OS and PFS. We defined the outcome of OS as the time from the date of initiation of treatments (ie, MIH, OH or RFA) to the date of death from any cause. We defined the outcome of PFS as the time from the date of initiation of treatments until the date of disease progression (eg, radiographic progression). The information regarding disease progression was obtained from the records in the Taiwan Cancer Registry. We applied an intention-to-treat (ITT) analysis and followed patients from the index date to the occurrence of study outcomes, death, or the end date of the database (31st January, 2020).

Covariates

We selected covariates based on published literature[23–25] and expert opinions. The covariates included demographics, laboratory data, concomitant prescription drugs, comorbidities, and healthcare utilization (Table 1). We collected data from 1-year prior to the index date to determine patients' baseline comorbidities and laboratory data. We collected data from 3 months prior to the index date regarding patients' co-medications. The details of the covariates are listed in Table S1.

Table 1 Baseline Characteristics of Study Cohorts After Propensity Score Matching

Number of patients, n	Main Analysis		aSMD	Main Analysis		aSMD	Control Analysis		aSMD
	MIH n=555	OH n=555		MIH n=382	RFA n=382		OH n=1114	RFA n=1114	
Demographics									
Age, years (mean ± SD)	67.20(11.30)	67.16(10.18)	0.00	69.23(10.59)	69.10(11.07)	0.01	71.26(9.90)	71.19(10.78)	0.01
Male sex, n (%)	414(74.59)	428(77.12)	0.06	280(73.30)	266(69.63)	0.08	815(73.16)	808(72.53)	0.01
Calendar year of index date, n (%)									
Before 2015	98(17.66)	97(17.48)	0.00	88(23.04)	88(23.04)	0.00	586(52.60)	591(53.05)	0.01
2015 or after	457(82.34)	458(82.52)	0.00	294(76.96)	294(76.96)	0.00	528(47.40)	523(46.95)	0.01
Smoke, n (%)	137(24.68)	128(23.06)	0.04	93(24.35)	108(28.27)	0.09	317(28.46)	312(28.01)	0.01
Alcohol, n (%)	78(14.05)	74(13.33)	0.02	51(13.35)	56(14.66)	0.04	209(18.76)	199(17.86)	0.02
Betel nut, n (%)	25(4.50)	30(5.41)	0.04	17(4.45)	21(5.50)	0.05	93(8.35)	101(9.07)	0.03
Stage (initial), n (%)									
0	126(22.70)	116(20.90)	0.04	97(25.39)	96(25.13)	0.01	250(22.44)	250(22.44)	0.00
A	366(65.95)	369(66.49)	0.01	239(62.57)	240(62.83)	0.01	673(60.41)	693(62.21)	0.04
B	63(11.35)	70(12.61)	0.04	46(12.04)	46(12.04)	0.00	191(17.15)	171(15.35)	0.05
Laboratory data									
BMI, n (%), kg/m^2									
≤18	7(1.26)	8(1.44)	0.02	5(1.31)	6(1.57)	0.02	16(1.44)	18(1.62)	0.01
18–24	232(41.80)	241(43.42)	0.03	148(38.74)	151(39.53)	0.02	442(39.68)	443(39.77)	0.00
≥24	313(56.40)	303(54.59)	0.04	226(59.16)	219(57.33)	0.04	634(56.91)	635(57.00)	0.00
Unknown	3(0.54)	3(0.54)	0.00	3(0.79)	6(1.57)	0.07	22(1.97)	18(1.62)	0.03
eGFR, n (%), mL/min/1.73m^2									
≤60	87(15.68)	91(16.40)	0.02	68(17.80)	75(19.63)	0.05	199(17.86)	197(17.68)	0.00
60–90	244(43.96)	214(38.56)	0.11	175(45.81)	159(41.62)	0.08	465(41.74)	467(41.92)	0.00
≥90	191(34.41)	204(36.76)	0.05	124(32.46)	137(35.86)	0.07	422(37.88)	423(37.97)	0.00
Unknown	33(5.95)	46(8.29)	0.09	15(3.93)	11(2.88)	0.06	28(2.51)	27(2.42)	0.00
HDL, n (%), mg/dl									
<40	50(9.01)	57(10.27)	0.04	39(10.21)	46(12.04)	0.05	100(8.98)	91(8.17)	0.03
≥40	127(22.88)	117(21.08)	0.04	98(25.65)	90(23.56)	0.04	177(15.89)	184(16.52)	0.01
Unknown	378(68.11)	381(68.65)	0.01	245(64.14)	246(64.40)	0.01	837(75.13)	839(75.31)	0.00
LDL, n (%), mg/dl									
<100	101(18.20)	94(16.94)	0.03	75(19.63)	76(19.90)	0.01	160(14.36)	150(13.46)	0.02
≥100	97(17.48)	100(18.02)	0.01	70(18.32)	71(18.59)	0.01	135(12.12)	134(12.03)	0.00
Unknown	357(64.32)	361(65.05)	0.01	237(62.04)	235(61.52)	0.01	819(73.52)	830(74.51)	0.02

(*Continued*)

Table 1 (Continued).

Number of patients, n	Main Analysis		aSMD	Main Analysis		aSMD	Control Analysis		aSMD
	MIH n=555	OH n=555		MIH n=382	RFA n=382		OH n=1114	RFA n=1114	
TG, n (%), mg/dl									
<150	122(21.98)	106(19.10)	0.07	70(18.32)	68(17.80)	0.01	153(13.73)	153(13.73)	0.00
≥150	31(5.59)	40(7.21)	0.07	17(4.45)	18(4.71)	0.01	41(3.68)	47(4.22)	0.03
Unknown	402(72.43)	409(73.69)	0.03	295(77.23)	296(77.49)	0.01	920(82.59)	914(82.05)	0.01
CEA, n (%), ng/mL									
<5	265(47.75)	278(50.09)	0.05	144(37.70)	151(39.53)	0.04	318(28.55)	305(27.38)	0.03
≥5	15(2.70)	15(2.70)	0.00	11(2.88)	12(3.14)	0.02	35(3.14)	43(3.86)	0.04
Unknown	275(49.55)	262(47.21)	0.05	227(59.42)	219(57.33)	0.04	761(68.31)	766(68.76)	0.01
AFP, n (%), ng/mL									
<20	274(49.37)	282(50.81)	0.03	201(52.62)	192(50.26)	0.05	580(52.06)	595(53.41)	0.03
≥20	191(34.41)	185(33.33)	0.02	123(32.20)	137(35.86)	0.08	435(39.05)	424(38.06)	0.02
Unknown	90(16.22)	88(15.86)	0.01	58(15.18)	53(13.87)	0.04	99(8.89)	95(8.53)	0.01
ALK, n (%), U/L									
<82	275(49.55)	280(50.45)	0.02	179(46.86)	199(52.09)	0.10	523(46.95)	521(46.77)	0.00
≥82	148(26.67)	154(27.74)	0.02	115(30.10)	121(31.68)	0.03	366(32.85)	372(33.99)	0.02
Unknown	132(23.78)	121(21.80)	0.05	88(23.04)	62(16.23)	0.17	225(20.20)	221(19.84)	0.01
AST, n (%), U/L									
<34	293(52.79)	287(51.71)	0.02	189(49.48)	184(48.17)	0.03	419(37.61)	429(38.51)	0.02
≥34	221(39.82)	217(39.10)	0.01	177(46.34)	184(48.17)	0.04	667(59.87)	659(59.16)	0.01
Unknown	41(7.39)	51(9.19)	0.07	16(4.19)	14(3.66)	0.03	28(2.51)	26(2.33)	0.01
ALT, n (%), U/L									
<36	307(55.32)	300(54.05)	0.03	211(55.24)	203(53.14)	0.04	528(47.40)	524(47.04)	0.00
≥36	210(37.84)	209(37.66)	0.00	156(40.84)	166(43.46)	0.05	559(50.18)	565(50.72)	0.01
Unknown	38(6.85)	46(8.29)	0.05	15(3.93)	13(3.40)	0.03	27(2.42)	25(2.24)	0.01
Other laboratory data									
DBI, n (%), mg/dl									
<0.4	431(77.66)	431(77.66)	0.00	266(69.63)	266(69.63)	0.00	539(48.38)	549(49.28)	0.02
≥0.4	31(5.59)	33(5.95)	0.02	31(8.12)	31(8.12)	0.00	141(12.66)	140(12.57)	0.00
unknown	93(16.76)	91(16.40)	0.01	85(22.25)	85(22.25)	0.00	434(38.96)	425(38.15)	0.02
TBI, n (%), mg/dl									
<1.2	413(74.41)	415(74.77)	0.01	284(74.35)	284(74.35)	0.00	748(67.15)	758(68.04)	0.02
≥1.2	46(8.29)	44(7.93)	0.01	34(8.90)	34(8.90)	0.00	179(16.07)	158(14.18)	0.05
unknown	96(17.30)	96(17.30)	0.00	64(16.75)	64(16.75)	0.00	187(16.79)	198(17.77)	0.03
BUN, n (%), mg/dl									
<20	351(63.24)	367(66.13)	0.06	244(63.87)	244(63.87)	0.00	771(69.21)	774(69.48)	0.01
≥20	102(18.38)	80(14.41)	0.11	88(23.04)	88(23.04)	0.00	190(17.06)	184(16.52)	0.01
unknown	102(18.38)	108(19.46)	0.03	50(13.09)	50(13.09)	0.00	153(13.73)	156(14.00)	0.01
CRP, n (%), mg/L									
<10	123(22.16)	122(21.98)	0.00	83(21.73)	83(21.73)	0.00	185(16.61)	167(14.99)	0.04
≥10	22(3.96)	22(3.96)	0.00	22(5.76)	22(5.76)	0.00	77(6.91)	94(8.44)	0.06
unknown	410(73.87)	411(74.05)	0.00	277(72.51)	277(72.51)	0.00	852(76.48)	853(76.57)	0.00
Uric acid, n (%), mg/dl									
<7	74(13.33)	95(17.12)	0.11	71(18.59)	71(18.59)	0.00	170(15.26)	162(14.54)	0.02
≥7	34(6.13)	33(5.95)	0.01	29(7.59)	29(7.59)	0.00	77(6.91)	80(7.18)	0.01
unknown	447(80.54)	427(76.94)	0.09	282(73.82)	282(73.82)	0.00	867(77.83)	872(78.28)	0.01
Concomitant prescription drugs, n (%)									
Glucocorticoids	237(42.70)	234(42.16)	0.01	140(36.65)	144(37.70)	0.02	389(34.92)	392(35.19)	0.01
NSAID	40(7.21)	29(5.23)	0.08	29(7.59)	35(9.16)	0.06	81(7.27)	93(8.35)	0.04
Antiplatelet agents	33(5.95)	33(5.95)	0.00	26(6.81)	32(8.38)	0.06	82(7.36)	76(6.82)	0.02
Anticoagulants	4(0.72)	4(0.72)	0.00	4(1.05)	4(1.05)	0.00	7(0.63)	6(0.54)	0.01
ACEIs/ARBs	75(13.51)	72(12.97)	0.02	60(15.71)	72(18.85)	0.08	155(13.91)	150(13.46)	0.01
β-blockers	35(6.31)	31(5.59)	0.03	32(8.38)	37(9.69)	0.05	99(8.89)	105(9.43)	0.02

(*Continued*)

Table 1 (Continued).

Number of patients, n	Main Analysis		aSMD	Main Analysis		aSMD	Control Analysis		aSMD
	MIH n=555	OH n=555		MIH n=382	RFA n=382		OH n=1114	RFA n=1114	
CCB	66(11.89)	68(12.25)	0.01	56(14.66)	56(14.66)	0.00	137(12.30)	126(11.31)	0.03
Nitrates	14(2.52)	14(2.52)	0.00	13(3.40)	16(4.19)	0.04	37(3.32)	33(2.96)	0.02
Statin	44(7.93)	49(8.83)	0.03	31(8.12)	30(7.85)	0.01	69(6.19)	68(6.10)	0.00
Ezetimibe	11(1.98)	6(1.08)	0.07	12(3.14)	6(1.57)	0.10	9(0.81)	13(1.17)	0.04
Fibrate	12(2.16)	9(1.62)	0.04	9(2.36)	6(1.57)	0.06	13(1.17)	19(1.71)	0.05
Silymarin	96(17.30)	94(16.94)	0.01	75(19.63)	83(21.73)	0.05	268(24.06)	276(24.78)	0.02
Diuretics	31(5.59)	18(3.24)	0.11	28(7.33)	23(6.02)	0.05	78(7.00)	77(6.91)	0.00
Insulin	16(2.88)	16(2.88)	0.00	11(2.88)	21(5.50)	0.13	29(2.60)	33(2.96)	0.02
Metformin	57(10.27)	50(9.01)	0.04	42(10.99)	49(12.83)	0.06	92(8.26)	100(8.98)	0.03
Comorbidities, n (%)									
T2DM	172(30.99)	180(32.43)	0.03	127(33.25)	145(37.96)	0.09	354(31.78)	391(35.10)	0.07
Hypertension	264(47.57)	246(44.32)	0.07	190(49.74)	196(51.31)	0.03	528(47.40)	518(46.50)	0.02
Hyperlipidemia	98(17.66)	92(16.58)	0.03	67(17.54)	59(15.45)	0.06	145(13.02)	154(13.82)	0.02
Ischemic heart disease	41(7.39)	34(6.13)	0.05	32(8.38)	32(8.38)	0.00	75(6.73)	73(6.55)	0.01
Cerebrovascular disease	19(3.42)	16(2.88)	0.03	15(3.93)	19(4.97)	0.05	57(5.12)	61(5.48)	0.02
COPD	26(4.68)	28(5.05)	0.02	21(5.50)	21(5.50)	0.00	74(6.64)	75(6.73)	0.00
CKD	53(9.55)	39(7.03)	0.09	40(10.47)	39(10.21)	0.01	88(7.90)	74(6.64)	0.05
Liver cirrhosis	425(76.58)	444(80.00)	0.08	326(85.34)	327(85.60)	0.01	998(89.59)	1021(91.64)	0.07
ARLD	23(4.14)	19(3.42)	0.04	22(5.76)	18(4.71)	0.05	53(4.76)	54(4.85)	0.00
Hepatitis B	303(54.59)	287(51.71)	0.06	174(45.55)	179(46.86)	0.03	468(42.01)	452(40.57)	0.03
Hepatitis C	181(32.61)	169(30.45)	0.05	145(37.96)	150(39.27)	0.03	438(39.32)	439(39.41)	0.00
CCI (mean ± SD)	3.76(1.55)	3.89(1.61)	0.00	4.00(1.60)	4.05(1.58)	0.00	4.04(1.54)	4.07(1.52)	0.00
Hospital level, n (%)									
Medical center	434(78.20)	437(78.74)	0.01	289(75.65)	287(75.13)	0.01	814(73.07)	813(72.98)	0.00
Regional hospital	121(21.80)	118(21.26)	0.01	93(24.35)	95(24.87)	0.01	300(26.93)	301(27.02)	0.00
District hospital	<3(0.00)	<3(0.00)	0.00	<3(0.00)	<3(0.00)	0.00	<3(0.00)	<3(0.00)	0.00

Abbreviations: MIH, minimally invasive hepatectomy; OH, open hepatectomy; RFA, radiofrequency ablation; aSMD, absolute standardized mean difference; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DBI, direct bilirubin; TBI, total bilirubin; BUN, blood urea nitrogen; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drug; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, Calcium channel blockers; T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ARLD, alcohol-related liver disease; CCI, Charlson comorbidity index.

Statistical Analysis

We used the mean ± standard deviation (SD) and proportions (%) to describe continuous and categorical variables, respectively. We calculated the absolute standardized mean difference (aSMD) to assess differences in the covariates between the two groups. aSMD values less than 0.2 indicate adequate balance in the covariates.[26,27] We calculated propensity scores by two separate multivariable logistic regressions for MIH vs OH and MIH vs RFA, conditional on all covariates listed in Table 1. To create more homogeneous groups for comparison, each patient in the MIH group was matched 1:1 to a patient in the OH and RFA groups.[27] The propensity score-matched method generated the comparisons between the groups based on average treatment effects.[27] We used greedy nearest neighbor matching to choose a treatment group member with the highest propensity score and then chose a control group member that was the closest match. We used Kaplan-Meier methods to evaluate adjusted survival probability from the time to survival outcomes. We used multivariable Cox proportional hazards models to obtain hazard ratios (HR) with 95% confidence intervals (CIs) between propensity score-matched groups. All analyses were performed using statistical software (SAS, version 9.4; SAS Institute, Inc., Cary, NC, USA).

Subgroup and Sensitivity Analyses

We conducted a series of analyses to examine the effects of treatments among different sub-cohorts and to test the robustness of the results. We stratified patients by different age groups (<65 or ≥65 years old), BCLC stages (stages 0 and A, or stage B) and hospital levels (medical or non-medical center) and repeated the analysis. Moreover, because MIH

treatment had been used extensively in CGMF since 2015, in order to minimize the effects of different time periods of treatments, we restricted our study period to the most recent 5 years (ie, from 2015–2019) for a sensitivity analysis.

Control Analysis

As a control analysis we compared the survival outcomes between patients receiving OH and patients receiving RFA. We hypothesized that patients receiving OH had better survival outcomes than those receiving RFA, based on previous studies.[28,29] The comparisons could help to identify residual confounders and to determine the internal validity of the study. We applied the same cohort inclusion and exclusion criteria, survival outcomes, and propensity score method for the comparison between OH and RFA.

Quantitative Bias Analyses

We calculated E-values to quantify the minimum strength of association that an unmeasured confounding factor would need to have with the exposure and the outcome, on a relative risk scale, in order to fully explain away our observed association between MIH and survival outcomes, based on the measured covariates.[30]

Results

Patient Characteristics

We identified 6037 HCC patients (559 patients for MIH with a mean age of 67.23 years and 74.78% male; 2685 patients for OH with a mean age of 68.37 years and 77.39% male; 2,793 patients for RFA with a mean age of 73.09 years and 62.94% male) based on the study inclusion and exclusion criteria. After applying 1:1 propensity score-matched analyses, we included 555, 382 and 1114 pairs of MIH vs OH, MIH vs RFA and OH vs RFA, respectively. The cohort selection is shown in Figure S1. Details of baseline characteristics of matched and original cohorts are listed in Table 1 and Table S2.

MIH vs OH

In the matched MIH vs OH cohort, the disease progression rates in the MIH and OH groups were 25.18% (139/552) and 29.48% (163/553), respectively, during a median follow-up of 30 months. 3-year and 5-year overall survival rates in the MIH group were 90.96% and 84.00% while 3-year and 5-year overall survival rates were 86.27% and 78.54% in the OH group. Patients initially receiving MIH were associated with an OS benefit, compared to those initially receiving OH with an HR of 0.62 (95% CI: 0.43–0.88, p value <0.05, E-value = 2.61). PFS risk was similar for patients receiving MIH and OH (HR: 0.92, 95% CI: 0.74–1.16, p value = 0.52, E-value = 1.39) (shown in Table 2).

Table 2 Evaluation of Overall Survival and Progression Free Survival Among Patients Receiving MIH, OH, and RFA

	Patients (n)	Events (n)	Person-Years	Incidence Rate (per 1,000 person-years)	Adjusted HR (95% CI)
Overall survival					
Main analysis					
MIH versus OH					
MIH	555	48	17,958	2.67	0.62 (0.43–0.88)
OH	555	87	20,328	4.28	Reference
MIH versus RFA					
MIH	382	41	13,488	3.04	0.46 (0.32–0.67)
RFA	382	85	13,162	6.46	Reference

(*Continued*)

Table 2 (Continued).

	Patients (n)	Events (n)	Person-Years	Incidence Rate (per 1,000 person-years)	Adjusted HR (95% CI)
Control analysis					
OH versus RFA					
OH	1,114	337	56,156	6.00	0.70 (0.61–0.81)
RFA	1,114	417	49,517	8.42	Reference
Progression free survival					
Main analysis					
MIH versus OH					
MIH	552	139	14,503	9.58	0.92 (0.74–1.16)
OH	553	163	16,741	9.74	Reference
MIH versus RFA					
MIH	379	109	10,599	10.28	0.48 (0.38–0.61)
RFA	379	190	8,319	22.84	Reference
Control analysis					
OH versus RFA					
OH	1,113	526	41,867	12.56	0.58 (0.52–0.65)
RFA	1,106	697	29,268	23.81	Reference

Abbreviations: MIH, minimally invasive hepatectomy; OH, open hepatectomy; RFA, radiofrequency ablation; HR, hazard ratio; CI, confidence interval.

MIH vs RFA

In the matched MIH vs RFA cohort, the disease progression rates in the MIH and RFA groups were 28.76% (109/379) and 50.13% (190/379), respectively, during a median follow-up of 32 months. 3-year and 5-year overall survival rates in the MIH group were 89.65% and 82.41% while 3-year and 5-year overall survival rates were 80.66% and 62.61% in the RFA group. Patients initially receiving MIH were associated with an OS and PFS benefit, compared to those initially receiving RFA, with HRs of 0.46 (95% CI: 0.32–0.67, p value <0.01, E-value = 3.77) and 0.48 (95% CI: 0.38–0.61, p value <0.01, E-value = 3.59), respectively (shown in Table 2).

OH vs RFA

In the matched OH vs RFA cohort, the disease progression rates in the OH and RFA groups were 47.26% (526/1113) and 63.02% (697/1106), respectively, during a median follow-up of 44 months. 3-year and 5-year overall survival rates in the OH group were 83.26% and 69.57% while 3-year and 5-year overall survival rates were 74.33% and 58.93% in the RFA group. Patients initially receiving OH were associated with an OS and PFS benefit, compared to those initially receiving RFA, with HRs of 0.70 (95% CI: 0.61–0.81, p value <0.01) and 0.58 (95% CI: 0.52–0.65, p value <0.01), respectively (shown in Table 2). The Kaplan-Meier curves for OS and PFS comparisons between different treatments are presented in Figures 1 and 2, respectively.

Subgroup and Sensitivity Analyses

We found the results of the subgroup analyses were generally consistent with the main analyses (shown in Figures S2 and S3). Patients receiving MIH in a non-medical center had numerically elevated risk of disease progression (HR: 1.27, 95% CI: 0.81–1.99); however, the hospital level vs treatment interaction analysis yielded no significant conclusion (p value = 0.06). There were also no statistically significant differences in OS for the subgroups of age <65 years, and BCLC stage B, in the comparison between MIH and OH. As for the sensitivity analysis with the study period restricted to the most recent 5 years, the results were robust in both the MIH vs OH and MIH vs RFA comparisons.

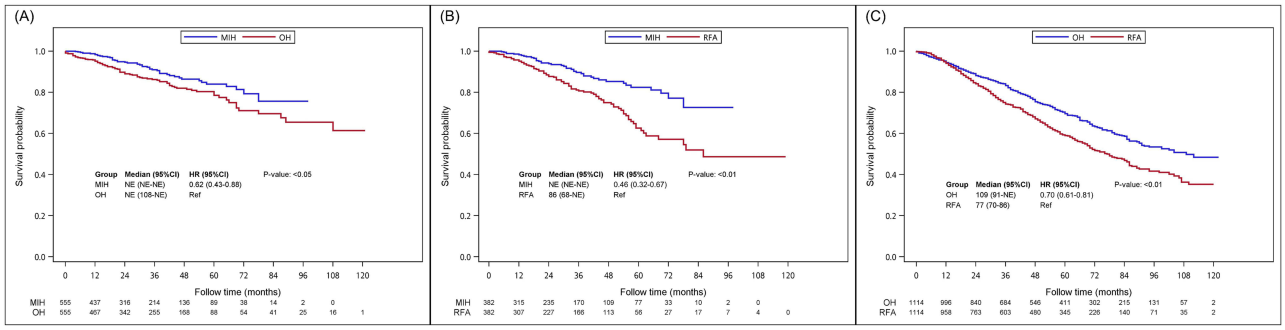

Figure 1 Comparison of overall survival in patients with early or intermediate-stage HCC between three matched cohorts: (**A**) MIH vs OH, (**B**) MIH vs RFA and (**C**) OH vs RFA.
Abbreviations: HCC, hepatocellular carcinoma; MIH, minimally invasive hepatectomy; OH, open hepatectomy; RFA, radiofrequency ablation; NE, not estimable.

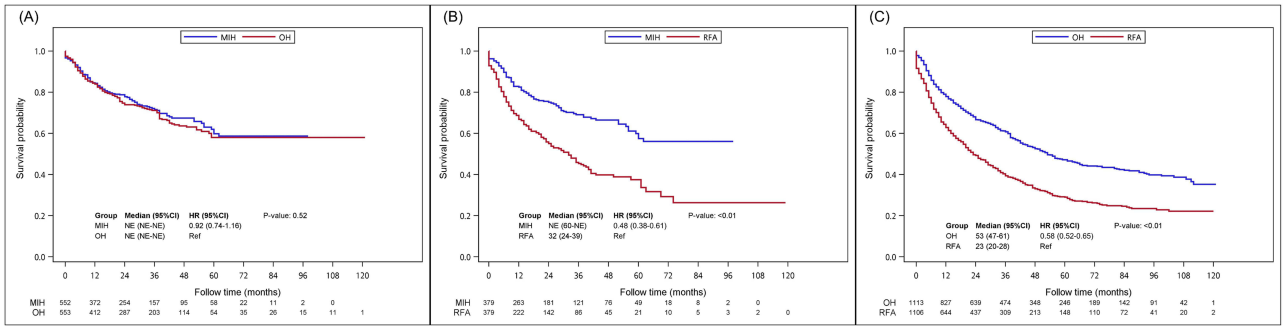

Figure 2 Comparison of progression free survival in patients with early or intermediate-stage HCC between three matched cohorts: (**A**) MIH vs OH, (**B**) MIH vs RFA and (**C**) OH vs RFA.
Abbreviations: HCC, hepatocellular carcinoma; MIH, minimally invasive hepatectomy; OH, open hepatectomy; RFA, radiofrequency ablation; NE, not estimable.

Discussion

This multi-institutional study found that MIH is superior to OH and RFA with regard to the survival outcomes in patients with early and resectable intermediate-stage HCC. The results remained consistent throughout a series of subgroup and sensitivity analyses, including stratifying patients by age, BCLC stage, and hospital level. The results of the control analysis were consistent with the hypothesis that patients receiving OH would have better survival outcomes than those receiving RFA, suggesting an appropriate validity of our analysis. To our knowledge, this is the largest study comparing MIH, OH and RFA head-to-head in real-world settings. Because our results indicated better survival outcomes with MIH, and given the nature of MIH resulting in less wound trauma and less intra-abdominal organ manipulation, we believe MIH could be prioritized in the treatment of early and resectable intermediate-stage HCC.

Although MIH has been applied widely in the resection of early and intermediate-stage HCC patients, its effectiveness has not been properly evaluated. A study by Lee et al[9] compared 33 patients who underwent MIH with 50 patients who underwent OH in a case-matched analysis, and found that MIH and OH have similar long term outcomes. Another single center analysis by Cheung et al[10] indicated better 5-year OS outcome for patients receiving MIH (n = 110), but no difference for the 5-year PFS outcome, compared to OH (n = 330). Nonetheless, these studies involved insufficient numbers of cases per center, resulting in potentially large random errors and unstable statistical analysis. A meta-analysis[11] including 15 retrospective studies with a total of 1238 patients (MIH: n = 485, OH: n = 753) suggested that there was no difference in OS and PFS outcomes between the MIH and OH groups. However, there was a high possibility of selection bias for some of the studies included in this meta-anaylsis.[31–36] These observational studies included in the meta-analysis did not apply randomization procedures or approaches like propensity score methods to achieve good exchangeability between patients in different treatment groups.[37] Hence, our study adopted propensity score methods to create more homogeneous groups with similar probabilities of treatment assignment to improve comparability. We found that MIH showed better overall survival and

comparable progression-free survival outcome, compared to OH, suggesting MIH has long term advantages over OH. Notably, in this study the disease progression rate and overall survival rate in patients with MIH were 25.18% and 91.35%, respectively, which appeared to be better than the rates reported in previous studies.[9,10] The likely explanation is that we included more patients with BCLC stage 0 (very early stage). This finding extended the knowledge that MIH could be superior to OH, even for patients with very early or early-stage HCC on account of its predictable long-term benefit.

One meta-analysis[14] found that patients receiving RFA had increased mortality rate and higher overall recurrence rate, compared to patients receiving MIH. Our study result was consistent with this meta-analysis. However, another meta-analysis[13] by Li et al yielded inconsistent results with a better 5-year OS but with no difference in 5-year PFS for those receiving MIH, compared to RFA. Since those receiving MIH and those receiving RFA may have different oncologic disease severity or baseline characteristics, confounding by indication should be carefully considered. Specifically, the treatment assignment for MIH or RFA was likely based on preoperative tumor findings, clinicians' specialties, surgeons' experience and hospital resources. For example, patients under the care of internal medicine departments tended to receive RFA, while those under the care of surgery departments were more likely to receive MIH. All of these factors, including the specialty of clinicians as aforementioned, were also associated with survival outcomes, highlighting the need to take these issues into consideration to avoid drawing spurious conclusions when comparing MIH and RFA. Therefore, we applied propensity score methods to create more homogeneous groups with similar characteristics for our comparisons. Moreover, we used a control analysis (OH versus RFA) to demonstrate that residual confounding effects were minor and should not affect the conclusion.

The MIH approach has several advantages over the OH and RFA approaches. MIH involves less wound trauma and less intra-abdominal organ manipulation. It also provides the caudal to cranial view, which is different from OH, and magnification (2X~10X) by the laparoscopic video system that allows critical structures to be seen clearly. All these benefits lead to a shorter hospital stay, and less blood loss, compared to OH.[38,39] However, the actual reasons for the superior OS and PFS of MIH are not fully explained in this study, namely that the reduced insult to the intra-peritoneal organs may produce less post-operative inflammation, while the reduced manipulation of the liver results in fewer tumor cells leaking out and pushing into systemic circulation.[40,41] Since the MIH approach provides not only the cosmetic benefit of smaller wound dissection, but also, based on our analysis, better survival outcomes, we believe the MIH approach should be incorporated as soon as possible and become a standard procedure with wider applications in the treatment of patients with early or resectable intermediate-stage HCC. A mandatory training system for young surgeons could also be considered in the near future to standardize MIH treatment.

There are some limitations in our study. First, although CGRD is the largest and a representative multi-institutional EHR database in Taiwan, it primarily includes an Eastern population. Given that the etiology and prognosis of HCC patients differ from those of the Western population,[42] future research focusing on people in Western countries, such as Europe and North America, is warranted. Second, our analysis did not consider the learning curve effects of clinicians, especially for MIH treatment, which was a relatively new treatment. We may therefore have underestimated the survival effects of MIH treatment on the survival outcomes. To address the issue, we conducted a post-hoc analysis comparing the survival outcomes of patients receiving MIH between those among the first 50 cases (when a clinician is less experienced) and the subsequent 50–100 cases (when a clinician is more experienced), based on data from one clinician in a hospital covered by CGRD. We found there was no difference in OS between the first 50 cases and subsequent 50–100 cases (shown in Figure S4), showing that the learning curve effect may be minor. Furthermore, our analysis may be subject to selection bias. However, a control analysis comparing survival outcomes between patients receiving OH and those receiving RFA, yielded results consistent with the hypothesized association, indicating that the possible selection bias may not have affected our conclusion substantially. Third, given the lack of molecular and pathological data in our database, we are unable to conduct analyses on treatment responses of different HCC subtypes. Nonetheless, we conducted a subgroup analysis based on the BCLC stage classification system which reflects distinct tumor recurrence patterns among patients. Finally, as in all studies using retrospective data, residual confounders may not have been fully eliminated. We found that the E-value of the main analysis comparing OS between MIH and RFA was 3.77, meaning that an unmeasured confounder would need to be large enough to have a 3.77 fold association with both exposure and outcome for it to change our conclusion. Hence it is unlikely that our conclusion can be explained away by an unmeasured confounder.

Conclusion

Our results indicated that MIH in patients with early or resectable intermediate-stage HCC was associated with better OS and PFS outcomes, compared to RFA. Compared to OH, MIH was associated with better OS, and similar PFS. The use of MIH may not only decrease the size of surgical incisions, but also offer better survival outcomes, as demonstrated by this study in real-life patients with early or resectable intermediate-stage HCC. Our study could thus provide strong grounds for future prospective studies to confirm the effectiveness of MIH.

Abbreviations

aSMD, absolute standardized mean difference; AFP, alpha-fetoprotein; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; CGMF, Chang Gung Medical Foundation; CGMH, Chang Gung Memorial Hospital; CGRD, Chang Gung Research Database; CI, confidence interval; CRP, C-reactive protein; DBI, direct bilirubin; eGFR, estimated glomerular filtration rate; EHR, electronic health record; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HR, hazard ratio; ICD, International Classification of Disease; ITT, intention-to-treat; LDL, low-density lipoprotein; MIH, minimally invasive hepatectomy; OH, open hepatectomy; OS, overall survival; PFS, progression free survival; RFA, radiofrequency ablation; SD, standard deviation; TBI, total bilirubin; TG, triglyceride.

Data Sharing Statement

Data analysis and management are permitted only within Chang Gung Memorial Hospitals in Taiwan. The SAS programs applied for this study and further information are available from the corresponding author on reasonable request.

Ethics Approval Statement

This study was conducted using data from the Chang Gung Research Database, with ethical approval granted by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (ID: 202001650B0). Our study complies with the Declaration of Helsinki. Relevant patient data were de-identified, and data analysis and management are permitted only within Chang Gung Memorial Hospitals in Taiwan. The data accessed complied with relevant data protection and privacy regulations. Therefore, the IRB determined that individual informed consent was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The abstract of this paper was presented at the ISPE's 14th Asian Conference on Pharmacoepidemiology (ACPE) as a poster presentation with interim findings. The authors report no other conflicts of interest in this work.

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