



# Liver stiffness in magnetic resonance elastography is prognostic for sorafenib-treated advanced hepatocellular carcinoma

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## Abstract

**Objective** We investigated whether liver stiffness (LS) quantified using magnetic resonance elastography (MRE) could predict the prognosis of advanced hepatocellular carcinoma (HCC) patients treated with sorafenib.

**Methods** We selected 50 sorafenib-treated advanced HCC patients who underwent MRE within 3 months before drug administration from a prospectively maintained cohort of chronic liver disease patients, according to the inclusion and exclusion criteria. Univariate and multivariate analyses were performed to evaluate the prognostic role of laboratory data, tumor characteristics, and MRE-assessed LS for overall survival (OS), progression-free survival (PFS), and significant liver injury (grade  $\geq 3$ ) after sorafenib administration.

**Results** High MRE-assessed LS either as continuous (per kPa, hazard ratio (HR) 1.54; 95% confidence interval (CI) 1.23–1.92,  $p < 0.001$ ) or categorical ( $> 7.5$  kPa, HR 4.06, 95% CI 1.40–11.79,  $p < 0.01$ ) variable was significantly associated with poor OS along with higher serum alpha-fetoprotein (AFP,  $\geq 400$  ng/mL) and advanced tumor stage (modified Union for International Cancer Control (mUICC) IVb). Higher MRE-assessed LS was also significantly associated with the development of significant liver injury after sorafenib administration (per kPa, HR 1.62, 95% CI 1.21–2.17,  $p = 0.001$ ;  $> 7.5$  kPa, HR 10.11, 95% CI 2.41–42.46,  $p = 0.002$ ). PFS analysis identified higher serum AFP ( $\geq 400$  ng/mL) and advanced tumor stage (mUICC IVb) as significant risk factors for early disease progression, whereas LS was not associated with PFS.

**Conclusion** Higher MRE-assessed LS is a potential biomarker for predicting poor OS and significant liver injury in advanced HCC patients treated with sorafenib.

## Key Points

- Higher pretreatment LS by MRE ( $> 7.5$  kPa), higher AFP ( $\geq 400$  ng/mL), and advanced tumor stage (mUICC IVb) were associated with poor OS in advanced HCC patients treated with sorafenib.
- Higher pretreatment LS by MRE was associated with developing significant (grade  $\geq 3$ ) liver injury during sorafenib treatment, which required termination of the therapy.
- Patients with high pretreatment LS by MRE should be monitored carefully for potential liver injury during sorafenib treatment.

**Keywords** Magnetic resonance elastography · Biomarker · Hepatocellular carcinoma · Sorafenib · Drug-induced liver injury

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## Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
ALT	Alanine transaminase
CI	Confidence interval
HCC	Hepatocellular carcinoma
HR	Hazard ratio
INR	International normalized ratio
LN	Lymph node
LS	Liver stiffness
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
mUICC	Modified Union for International Cancer Control
OS	Overall survival
PFS	Progression-free survival
ROI	Region of interest
SE	Standard error

## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the fourth leading cause of cancer-related mortality worldwide [1–3]. HCC with extrahepatic metastasis (M1 or N1) or locally advanced disease not amenable to locoregional therapy is considered an advanced stage [4–6]. Generally, advanced HCC patients demonstrate extremely poor prognosis with a median overall survival (OS) of 6–9 months [2, 7, 8]. Sorafenib, an oral multi-tyrosine kinase inhibitor, is the first regulatory-approved systemic therapeutic agent for advanced HCC patients [2, 8] and has been used as first-line therapy for these patients since 2006 [4–6].

Sorafenib targets vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and the Raf family; it has demonstrated significant anticancer effects against HCC [9]. Although sorafenib is a widely used treatment option for advanced HCC, its clinical benefit in terms of OS is modest at only an average of approximately 3 months [8]. Because the clinical response to sorafenib is often variable and unpredictable, reliable biomarkers are urgently needed for predicting its efficacy and safety in candidate advanced HCC patients.

Sorafenib-induced liver injury mainly develops as idiosyncratic hepatotoxicity [10]. Most patients with preserved liver function recover even after the hepatotoxicity. However, in advanced HCC patients whose underlying liver function is impaired, even minor hepatocellular damage could cause irreversible liver damage [11]. Therefore, it is necessary to establish a treatment plan by identifying high-risk patients with impaired liver function who may experience serious adverse events caused by sorafenib-induced liver injury.

Magnetic resonance elastography (MRE) is a non-invasive, magnetic resonance imaging (MRI)-based tool for the quantitative assessment of liver stiffness (LS) [12, 13]. MRE is considered the most accurate non-invasive technique for staging liver fibrosis [13]. Recently, it has been highlighted as a potential radio-omics biomarker for predicting the prognosis of patients with chronic liver disease and HCC [14–16]. However, the clinical implications of pretreatment LS by MRE in sorafenib-treated advanced HCC patients have not been explored.

Thus, we aimed to identify the clinical significance of LS by MRE in sorafenib-treated advanced HCC patients. We analyzed whether LS by MRE before sorafenib administration could be an independent biomarker for predicting OS or progression-free survival (PFS). We also analyzed whether pretreatment MRE-assessed LS could predict significant liver injury (grade  $\geq 3$ ) after sorafenib administration.

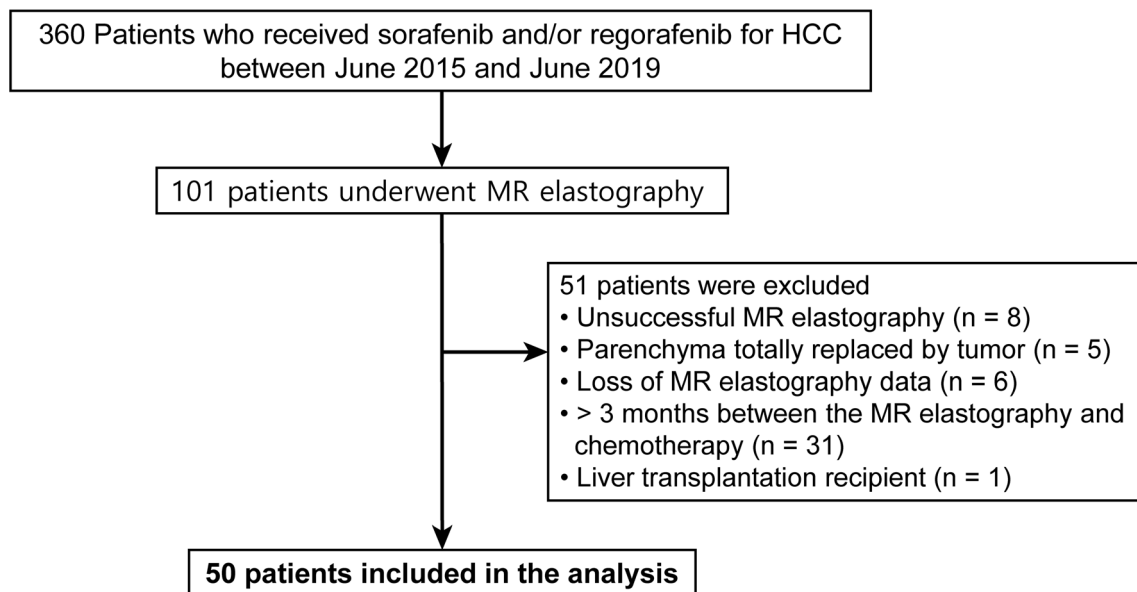
## Material and methods

### Patient selection

The institutional review board approved this retrospective study and waived the informed consent requirement (AJIRB-MED-MDB-18-484). Between June 2015 and June 2019, 360 advanced HCC patients treated with sorafenib were identified from a prospectively maintained cohort of chronic liver disease patients who underwent MRE. Among them, 101 patients underwent MRE before the first sorafenib treatment. Fourteen patients with unsuccessful MRE acquisition owing to ascites, large abdominal girth, or mechanical failure ( $n = 8$ ) and loss of MRE data ( $n = 6$ ) were excluded. Furthermore, we excluded patients with (a) MRE acquired more than 3 months before treatment ( $n = 31$ ), (b) hepatic parenchyma totally replaced by tumor ( $n = 5$ ), and (c) prior liver transplantation ( $n = 1$ ). Finally, 50 patients were included in the analysis (Fig. 1).

### MRE measurement of LS

MRE was performed as part of the baseline liver MRI using 1.5-T (Signa HDxt; GE Healthcare) and 3-T (Discovery 750w; GE Healthcare) scanners. Hepatic shear wave was induced by 60-Hz acoustic waves transmitted via passive driver and was imaged with motion-sensitized 2D gradient echo and 2D spin echo-echo planar pulse sequences in 1.5-T and 3-T scanners, respectively, in four contiguous image slices. Stiffness maps were generated for each image slice using inversion algorithm provided by a commercially available MRE package (MR Touch, GE Healthcare) [17]. The detailed MRE parameters are provided in Supplementary Table 1.



**Fig. 1** Flow chart demonstrating the inclusion and exclusion criteria for patient selection. HCC, hepatocellular carcinoma; MR, magnetic resonance

One abdominal radiologist (4 years of experience in liver MRE) measured the LS using a dedicated post-processing software program (READY View, version 12.3; GE Healthcare). The region of interest (ROI) was manually drawn on the stiffness map bounded by 95% confidence map while avoiding incoherent shear waves, large vessels, and tumors. The ROI was drawn 2–3 cm away from the tumor by referring to anatomic images to exclude tumor-bearing parenchyma [14]. The measured stiffness of four ROIs was averaged to represent the LS of the patient.

### Treatment of HCC, assessment of outcomes, and term definition

HCC was diagnosed based on the American Association for the Study of Liver Diseases (AASLD) practice guideline and the European Association for the Study of the Liver guideline [4, 18, 19]. The patients received sorafenib 400 mg twice daily until the occurrence of disease progression or sorafenib-induced adverse events. Following adverse event occurrence, the sorafenib dose was modified or stopped according to the type of adverse event and grade of severity. Multiphasic liver computed tomography was performed every 2–3 months after the initiation of sorafenib administration to evaluate treatment response. All patients with chronic hepatitis B were treated with antiviral agents during the follow-up period based on the guideline [20].

The following medical data were collected: sex, age, pre-existing underlying diseases including diabetes, Child-Pugh class, previous history of HCC treatment, tumor number, tumor size, vascular invasion, extrahepatic metastasis, HCC stage according to the modified Union for International Cancer Control (mUICC) criteria [21], duration of sorafenib treatment, and

adverse events during sorafenib treatment (including hand-foot skin reaction, diarrhea, and liver injury). The tumor size was measured by its largest diameter in centimeters. In case of multiple tumors, the size of the largest tumor was measured. The baseline laboratory data collected were platelet count, total bilirubin, albumin, alanine transaminase (ALT), international normalized ratio (INR) of prothrombin time, and alpha-fetoprotein (AFP) levels. Tumor response was evaluated by one of the four attending radiologists according to the modified Response Evaluation Criteria in Solid Tumors [22].

Adverse events associated with sorafenib treatment were monitored using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 [23]. The severity of liver injury after sorafenib administration was assessed using the grading system of the Drug-Induced Liver Injury Network [24]. PFS and OS were defined as the time from the initiation of sorafenib administration to disease progression and death from any cause, respectively. The time to termination of sorafenib owing to significant liver injury was defined as the time of sorafenib administration until drug cessation owing to the development of grade  $\geq 3$  liver injury.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) (version 20.0; SPSS Inc.) and R software package (R, version 3.2.5; R Foundation for Statistical Computing). The Kolmogorov-Smirnov test was performed to test the normality of continuous variables. Continuous variables with normal distribution were presented as mean  $\pm$  standard deviation, while non-normal variables were reported as median (interquartile range). To compare baseline characteristics between the groups, an independent

*t* test and chi-square test were used for continuous and categorical variables, respectively. For survival analysis, the Kaplan-Meier analysis with log-rank test was performed. Patients were divided into two groups according to the value of MRE-assessed LS (high or low) for the Kaplan-Meier analysis.

Because there was no established clinical information on cutoff values of MRE-assessed LS in advanced HCC, binary cutoff values were determined based on the best Youden's index on the receiver operating characteristic curve of OS. To identify risk factors associated with poor PFS and OS and shorter time to termination of sorafenib owing to grade  $\geq 3$  liver injury, univariate and multivariate Cox regression analyses were performed. In multivariate Cox regression analysis, multiple statistical models were derived using various combinations of the variables; the final model was determined, considering the discrimination power by concordance index. *P* values  $< 0.05$  (two-sided) were considered significant.

## Results

### Baseline characteristics and treatment outcomes

Table 1 shows the patient baseline characteristics. Study patients (age,  $61.9 \pm 11.3$  years) consisted of 40 men (90%) and 10 women (10%); 39 (78.0%) and 11 (22.0%) had Child-Pugh class A and B status, respectively. Thirty-five (70%) and 15 (30%) patients were categorized into mUICC stages IVa and IVb. Twenty-three patients (46%) experienced diarrhea or hand-foot syndrome or both after sorafenib administration; 8 (16%) experienced grade 3 adverse events.

ALT levels were elevated in 30 (60%) patients, including 18 (34%) with grade 1 liver injury who showed only a mild, transient increase without constitutional symptoms, which was resolved without interrupting sorafenib. However, 12 (24%) patients with grade  $\geq 3$  liver injury demonstrated impaired liver function with total bilirubin  $\geq 2.5$  mg/dL, requiring hospitalization and sorafenib termination. Only conservative care was available for all 12 patients after they developed liver injury because their hepatic function and performance status did not recover subsequently. The mean MRE-assessed LS was  $5.48 \pm 2.07$  kPa. Cutoff value of MRE-assessed LS for poor OS was determined as 7.5 kPa. Among the 50 patients, 43 patients (86%) showed LS  $\leq 7.5$  kPa, while 7 patients (14%) showed LS  $> 7.5$  kPa.

### Risk factors associated with poor OS

OS analysis was performed for all included patients using mortality data obtained from the Central Cancer Registry database of the National Cancer Center. The median OS was 155

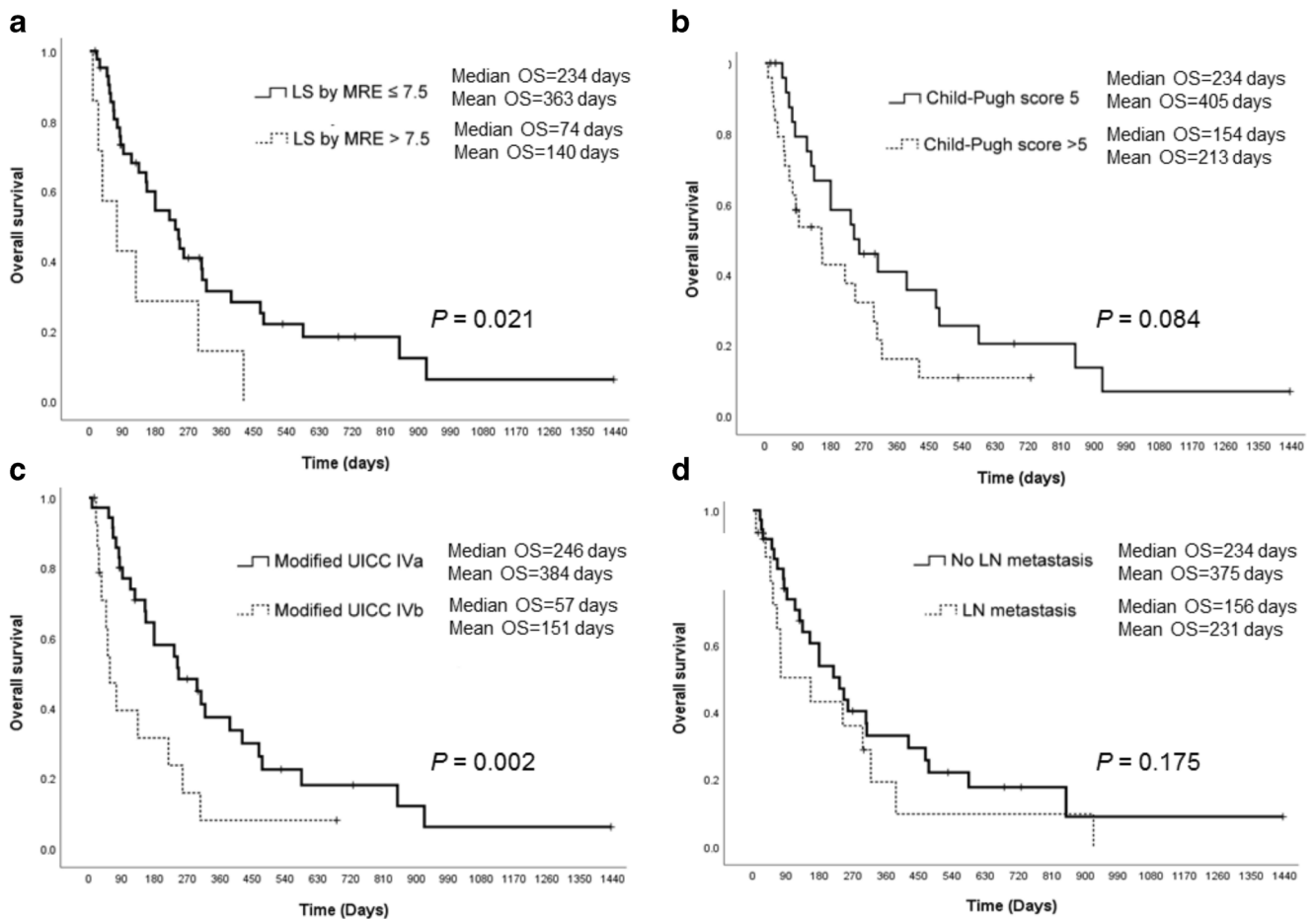
**Table 1** Baseline characteristics and treatment outcomes

Variable	All patients ( <i>n</i> = 50)
Age (years), mean $\pm$ standard deviation	61.9 $\pm$ 11.3
Male sex, <i>n</i> (%)	45 (90.0)
Child-Pugh class, <i>n</i> (%)	
A/B, <i>n</i> (%)	39/11 (78.0/22.0)
Platelet ( $\times 10^9$ /L), mean $\pm$ standard deviation	183.30 $\pm$ 97.59
Albumin, mean $\pm$ standard deviation (g/L)	3.87 $\pm$ 0.56
Bilirubin, mean $\pm$ standard deviation (mg/dL)	1.14 $\pm$ 1.02
AFP, median (interquartile range) (ng/mL)	410.7 (4764.7)
ALT, mean $\pm$ standard deviation (U/L)	48.62 $\pm$ 53.05
INR, mean $\pm$ standard deviation	1.19 $\pm$ 0.11
Underlying liver disease, <i>n</i> (%)	
CHB/CHC/allocoholics/cryptogenic	37 (74)/4 (8)/5 (10)/4 (8)
Tumor size, mean $\pm$ standard deviation (cm)	9.69 $\pm$ 4.58
mUICC stage, <i>n</i> (%)	
III/IVa/IVb	2 (4)/33 (66)/15 (30)
Portal vein invasion, yes, <i>n</i> (%)	44 (88)
LN metastasis, present, <i>n</i> (%)	15 (30)
Extrahepatic metastasis, present, <i>n</i> (%)	15 (30)
Previous therapy, <i>n</i> (%)	14 (28)
Transarterial chemoembolization	12 (24)
Intra-arterial infusion chemotherapy	2 (4)
Adverse effect of sorafenib, <i>n</i> (%)	
Diarrhea (grades 1, 2/3, 4)	4 (8)/4 (8)
Hand-foot syndrome (grades 1, 2/3, 4)	5 (10)/2 (4)
Both (grades 1, 2/3, 4)	6 (12)/2 (4)
Liver injury after sorafenib administration (grade 1/2/3/4/5)	18 (34)/0/6 (12)/5 (10)/1 (2)
MRE-assessed LS (kPa), mean $\pm$ standard deviation	5.48 $\pm$ 2.07
MRE-assessed LS (kPa) $> 7.5$ , <i>n</i> (%)	7 (14)

AFP alpha-fetoprotein, ALT alanine transaminase, INR international normalized ratio, CHB chronic hepatitis B, CHC chronic hepatitis C, mUICC modified Union for International Cancer Control, LN lymph node, LS liver stiffness, MRE magnetic resonance elastography

days with a range of 8–1435 days. The Kaplan-Meier analysis was performed to identify risk factors associated with poor OS; the curves were constructed (Fig. 2). In the Kaplan-Meier analysis, patients with higher MRE-assessed LS ( $> 7.5$  kPa) demonstrated a significantly poorer OS than those with lower LS ( $\leq 7.5$  kPa) ( $p = 0.021$ ). In addition to higher MRE-assessed LS, advanced tumor stage (mUICC IVb) was also identified as a risk factor for poor OS ( $p = 0.002$ ).

In the univariate Cox regression analysis, advanced tumor stage (mUICC IVb) and higher MRE-assessed LS ( $> 7.5$  kPa) were identified as significant risk factors for poor OS (Table 2). Multivariate Cox regression analysis was



**Fig. 2** Kaplan-Meier analysis comparing overall survival (OS) according to (a) liver stiffness (LS) assessed using magnetic resonance elastography (MRE), (b) Child-Pugh score, (c) modified Union for International Cancer Control (mUICC) stage, and (d) lymph node (LN) metastasis

performed with backward stepwise model selection (Table 2). Model 1 included MRE-assessed LS as a continuous variable,

whereas model 2 included MRE-assessed LS as a categorical variable using the cutoff value of 7.5 kPa.

**Table 2** Univariate and multivariate analyses of variables associated with overall survival (OS) in patients with hepatocellular carcinoma (HCC) treated with sorafenib

Factors	Univariate		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Sex, male	1.04 (0.36–2.65)	0.949	4.11 (1.12–15.06)	0.033	3.06 (0.81–11.57)	0.099
Age, years	1.02 (0.99–1.06)	0.182	1.04 (1.00–1.08)	0.029		
Child-Pugh score, ≥6	1.76 (0.91–3.38)	0.090			2.25 (0.99–5.15)	0.054
Platelet, < 100 (× 10 <sup>9</sup> /L)	0.64 (0.25–1.67)	0.364	2.65 (0.86–8.21)	0.91		
Albumin, ≤ 3.5 g/L	1.41 (0.62–3.23)	0.413			2.79 (0.87–8.94)	0.084
ALT, > 40 IU/L	1.72 (0.88–3.34)	0.113			2.28 (1.09–4.77)	0.029
AFP, ≥ 400 ng/mL	1.33 (0.70–2.52)	0.391	2.89 (1.29–6.47)	0.010	2.34 (1.04–5.27)	0.040
mUICC IVb	2.44 (1.22–4.91)	0.012	6.10 (2.45–15.17)	< 0.001	5.04 (2.03–12.54)	< 0.001
LS by MRE, kPa	1.14 (0.96–1.36)	0.126	1.54 (1.23–1.92)	< 0.001		
MRE-assessed LS > 7.5 kPa	2.40 (1.04–5.53)	0.039			4.06 (1.40–11.79)	0.010

Model 1: Harrell’s C index = 0.746 (standard error estimates = 0.043); model 2: Harrell’s C index = 0.750 (standard error estimates = 0.045)

HR hazard ratio, CI confidence interval, ALT alanine transaminase, AFP alpha-fetoprotein, mUICC modified Union for International Cancer Control, LS liver stiffness, MRE magnetic resonance elastography

In model 1, male sex, advanced age, higher AFP ( $\geq 400$  ng/mL), and advanced tumor stage (mUICC IVb) were identified as independent risk factors in addition to MRE-assessed LS (kPa, hazard ratio (HR) 1.54, 95% confidence interval (CI) 1.23–1.92,  $p < 0.001$ ). In model 2, higher MRE-assessed LS ( $> 7.5$  kPa, HR 4.06, 95% CI 1.40–11.79,  $p = 0.010$ ) was also revealed as an independent risk factor for poor OS along with higher AFP ( $\geq 400$  ng/mL), higher ALT ( $> 40$  IU/L), and advanced tumor stage (mUICC IVb). Harrell's C index values were calculated as 0.746 (standard error (SE) estimate = 0.043) for model 1 and 0.75 (0.045) for model 2, indicating sufficient discrimination power of the model.

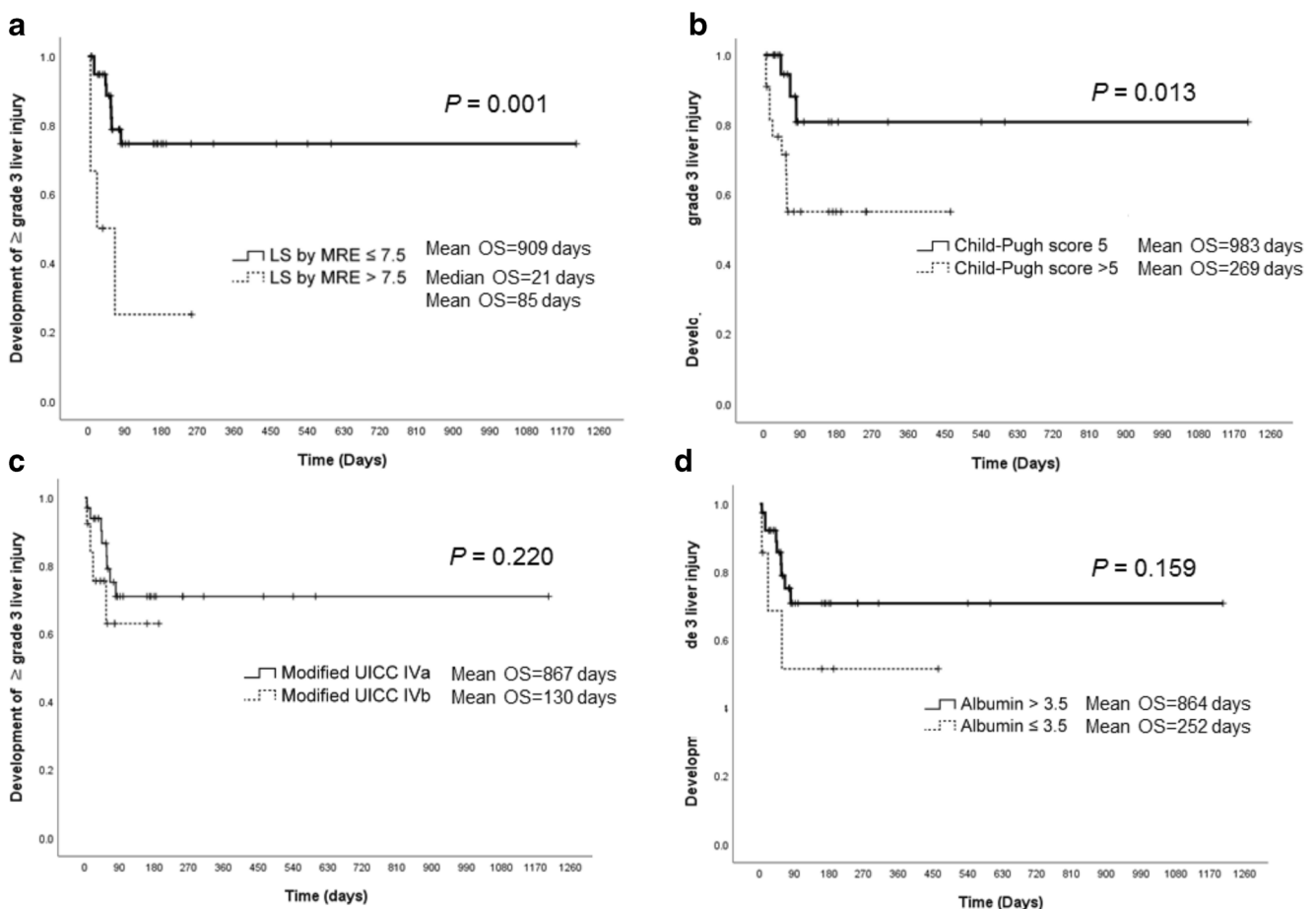
### Risk factors associated with development of grade $\geq 3$ liver injury

Four of the 50 patients were transferred to other hospitals before the sorafenib toxicity assessment. Therefore, the adverse effects of sorafenib were evaluated in 46 patients. Figure 3 shows comparisons of Kaplan-Meier curves for developing significant liver injury between groups divided according to MRE-assessed LS, Child-Pugh score, tumor stage,

and serum albumin level. Patients with higher baseline MRE-assessed LS ( $> 7.5$  kPa) or higher Child-Pugh score ( $\geq 6$ ) showed significantly earlier development of grade  $\geq 3$  liver injury than those with lower LS or Child-Pugh score ( $p = 0.001$  and  $p = 0.013$ , respectively).

Univariate Cox regression analysis revealed that higher Child-Pugh score ( $\geq 6$ ) and MRE-assessed LS ( $> 7.5$  kPa) were significant risk factors associated with earlier development of grade  $\geq 3$  liver injury (Table 3). Both the continuous and categorical variables ( $\leq 7.5$  kPa vs.  $> 7.5$  kPa) of MRE-assessed LS were significantly associated with the development of liver injury in the univariate analysis. For the adjustment of confounding variables, multivariate analysis was performed. In model 1, MRE-assessed LS was included as a continuous variable, whereas it was included as a categorical variable in model 2. In the multivariate model 1, high MRE-assessed LS (kPa, HR 1.62, 95% CI 1.21–2.17,  $p = 0.001$ ) was identified as the only significant risk factor for predicting the development of grade  $\geq 3$  liver injury (Table 3).

Harrell's C index of model 1 was 0.814, indicating the good discriminatory power of the model. In the Cox model



**Fig. 3** Kaplan-Meier analyses comparing the development of grade  $\geq 3$  liver injury according to (a) liver stiffness (LS) assessed using magnetic resonance elastography (MRE), (b) Child-Pugh score, (c) modified Union for International Cancer Control (mUICC) stage, and (d) serum albumin level

**Table 3** Univariate and multivariate analyses of variables associated with significant liver injury after sorafenib administration in patients with hepatocellular carcinoma (HCC)

Factors	Univariate		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Gender, male	1.76 (0.23–13.68)	0.590	4.57 (0.55–38.23)	0.161	7.26 (0.71–73.92)	0.094
Age, years	0.99 (0.94–1.06)	0.977				
Child-Pugh score, $\geq 6$	3.85 (1.04–14.26)	0.043	2.76 (0.72–10.62)	0.139	5.09 (1.28–20.19)	0.021
Platelet, $< 100 (\times 10^9/L)$	1.36 (0.36–5.04)	0.644				
Albumin, $\leq 3.5$ g/L	2.14 (0.58–7.93)	0.254				
ALT, $> 40$ IU/L	1.28 (0.41–4.06)	0.670				
AFP, $\geq 400$ ng/mL	1.07 (0.35–3.34)	0.902				
mUICC, IVb	1.82 (0.54–6.13)	0.333				
MRE-assessed LS, kPa	1.59 (1.21–2.10)	0.001	1.62 (1.21–2.17)	0.001		
MRE-assessed LS, $> 7.5$ kPa	1.59 (1.21–2.10)	0.001			10.11 (2.41–42.46)	0.002

Model 1: Harrell's C index = 0.814 (standard error estimates = 0.071); model 2: Harrell's C index = 0.747 (standard error estimates = 0.072)

HR hazard ratio, CI confidence interval, ALT alanine transaminase, AFP alpha-fetoprotein, mUICC modified Union for International Cancer Control, LS liver stiffness, MRE magnetic resonance elastography

2, sex (male), Child-Pugh score ( $\geq 6$ ), and MRE-assessed LS ( $> 7.5$  kPa) were finally selected for the multivariate Cox model. Higher MRE-assessed LS ( $> 7.5$  kPa, HR 10.11, 95% CI 2.41–42.46,  $p = 0.002$ ) and higher Child-Pugh score ( $\geq 6$ , HR 5.09, 95% CI 1.28–20.19,  $p = 0.021$ ) were identified as independent risk factors for predicting significant liver injury after sorafenib administration. Harrell's C index of model 2 was calculated as 0.747. The Kaplan-Meier analysis was performed to compare the OS between patients with grade  $\leq 2$  or without liver injury and patients with grade  $\geq 3$  liver injury (Supporting Fig. 1). The results indicated that patients with grade  $\geq 3$  liver injury demonstrated markedly poorer OS than those with grade  $\leq 2$  or without liver injury ( $p < 0.001$ ).

### Risk factors associated with poor PFS

PFS analysis was conducted in 32 patients following the exclusion of 4 who were transferred to other hospitals; sorafenib was discontinued in 14 patients before the first response evaluation because of grade  $\geq 3$  adverse events. Figure 4 shows comparisons of Kaplan-Meier survival curves of PFS between groups classified according to pretreatment tumor stage, MRE-assessed LS, serum AFP, and status of lymph node (LN) metastasis. Patients with mUICC stage IVb showed significantly earlier HCC progression than those with mUICC stage IVa in the Kaplan-Meier analysis ( $p = 0.038$ ).

In the univariate and multivariate Cox regression analysis, advanced tumor stage (mUICC IVb, HR 5.70, 95% CI 1.82–17.81,  $p = 0.001$ ) and presence of LN metastasis (present, HR 2.57, 95% CI 1.07–6.14,  $p = 0.035$ ) (Table 4) were revealed as independent risk factors for predicting poor PFS. MRE-assessed LS was not a significant predictor in the analysis of PFS.

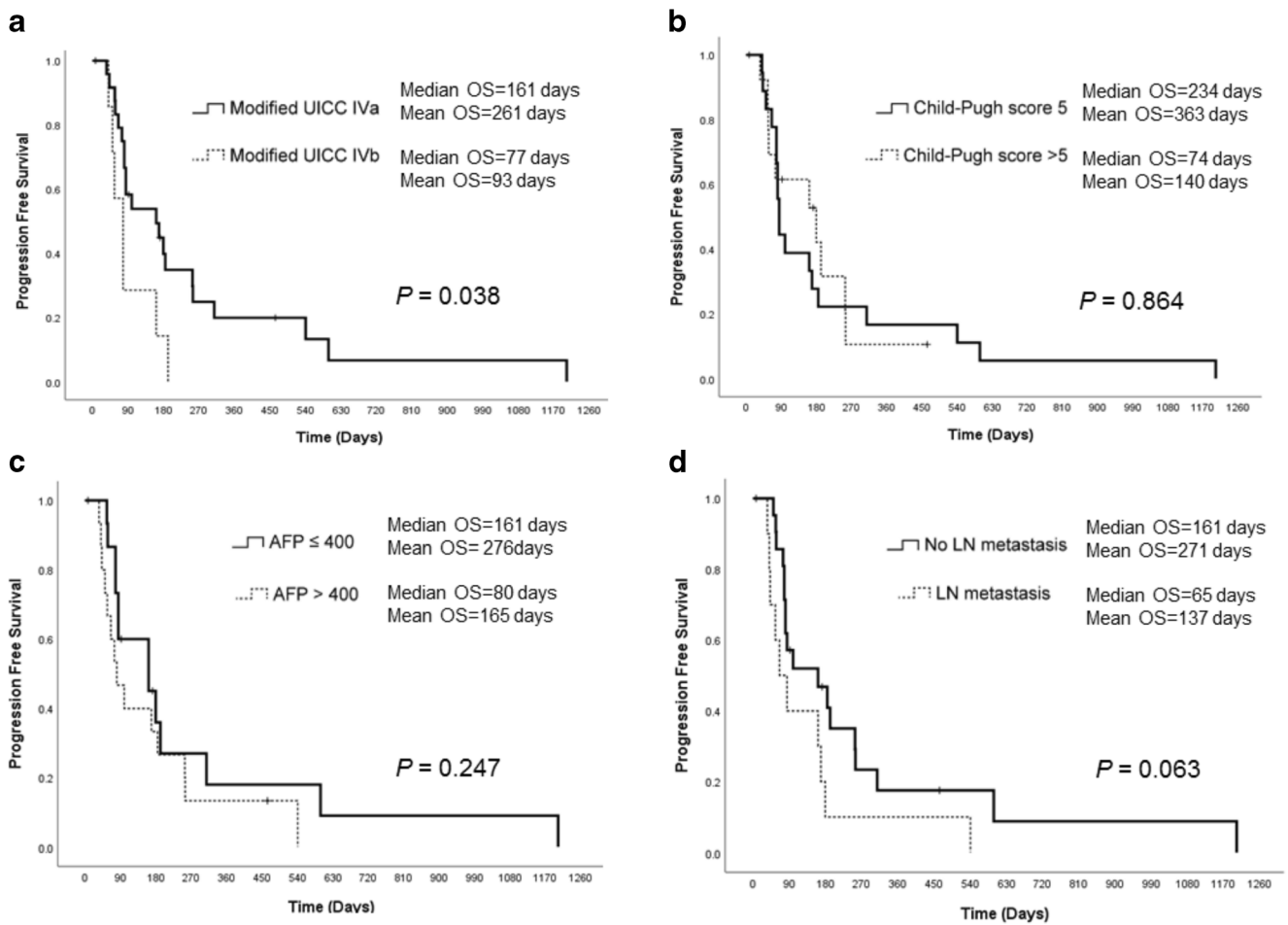
### Correlation analysis between clinical variables and MRE-assessed LS

To determine the correlation between clinical variables and MRE-assessed LS, Pearson correlation coefficients were calculated (Table 5). The MRE-assessed LS showed significant negative and positive correlations with serum albumin and bilirubin (Pearson  $R = -0.478$  and 0.487, respectively; both  $p < 0.001$ ) (Fig. 5).

### Discussion

In this study, the prognostic implications of MRE-assessed LS were explored in advanced HCC patients treated with sorafenib. A higher pretreatment MRE-assessed LS was strongly associated with poor OS in these patients along with traditional predictors such as advanced tumor stage and high AFP; it was also significantly associated with the development of grade  $\geq 3$  liver injury after sorafenib administration. To our knowledge, this is the first study to report these associations.

In the present study, 30 (60%) patients experienced liver injury after sorafenib administration. Among them, 18 patients had only transient and mild elevation of ALT, which was normalized without discontinuation of sorafenib. However, 12 (24%) patients demonstrated marked hepatic impairment with elevated total bilirubin  $> 2.5$  mg/dL that required hospitalization and drug termination, leading to a shorter OS than that of the patients with milder liver injury. In clinical trials, including the SHARP and Asia-Pacific trials, severe liver injury after sorafenib administration was reported as an uncommon adverse event [2, 5]. However, in this study,



**Fig. 4** Kaplan-Meier analyses comparing progression-free survival (PFS) according to (a) modified Union for International Cancer Control (mUICC) stage, (b) Child-Pugh score, (c) serum alpha-fetoprotein (AFP) level, and (d) lymph node (LN) metastasis status

**Table 4** Univariate and multivariate analyses of the variables associated with progression-free survival in patients with hepatocellular carcinoma treated with sorafenib

Factors	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Sex, male	0.72 (0.24–2.10)	0.544		
Age, years	1.01 (0.97–1.06)	0.581		
Child-Pugh score, ≥ 6	0.89 (0.40–1.98)	0.773		
Platelet, < 100 (× 10 <sup>9</sup> /L)	1.18 (0.44–3.16)	0.746		
Albumin, ≤ 3.5 g/L	1.46 (0.43–4.90)	0.539		
ALT, > 40 IU/L	1.34 (0.59–3.05)	0.492		
AFP, ≥ 400 ng/mL	1.59 (0.72–3.52)	0.254	2.26 (0.85–6.00)	0.102
LN metastasis, present	2.05 (0.92–4.55)	0.080	2.57 (1.07–6.14)	0.035
mUICC, IVb	2.65 (1.07–6.58)	0.035	5.70 (1.82–17.81)	0.001
MRE-assessed LS, kPa	0.94 (0.74–1.20)	0.612		
MRE-assessed LS, > 7.5 kPa	1.08 (0.25–4.63)	0.921		

Harrell’s C index = 0.767 (standard error estimates = 0.059)

HR hazard ratio, CI confidence interval, ALT alanine transaminase, AFP alpha-fetoprotein, LN lymph node, mUICC modified Union for International Cancer Control, LS liver stiffness, MRE magnetic resonance elastography



**Table 5** Pearson correlation analyses between clinical factors and liver stiffness measured using magnetic resonance elastography (MRE)

	MRE	<i>p</i> value
Albumin (g/dL)	−0.474**	<0.001
Bilirubin (mg/dL)	0.487**	<0.001
INR	0.203	0.162
Size (cm)	0.016	0.913

\*\*Correlation is significant at the 0.01 level (2-tailed)

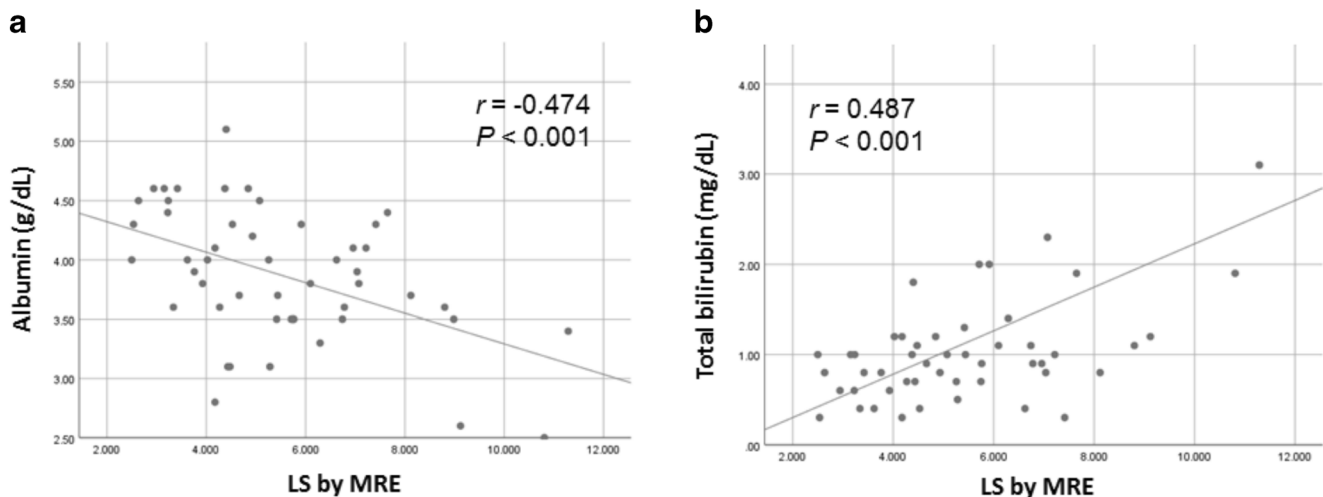
INR international normalized ratio

grade  $\geq 3$  liver injury occurred in 24% of sorafenib-treated patients. Similarly, several real-world studies reported the prevalence of sorafenib-induced severe liver injury as 18–24% [25–27]. Ozenne et al [25] reported that 26% of sorafenib-treated patients experienced grade 3 or 4 liver injury. In a retrospective study in Japan, liver failure occurred in 19% of sorafenib-treated HCC patients [26], which suggests that sorafenib-induced severe liver injury is not a rare adverse event and is strongly associated with poor OS of HCC patients. Thus, sorafenib-induced liver injury risk assessment in determining optimum treatment strategies is essential to improve prognosis of advanced HCC patient.

High MRE-assessed LS was identified as a potent independent biomarker for predicting severe liver injury after sorafenib administration. Patients with pretreatment LS  $> 7.5$  kPa demonstrated a more markedly increased risk of severe liver injury than that of patients with LS  $\leq 7.5$  kPa (HR 10.11). Thus, patients with LS  $> 7.5$  kPa should be monitored very carefully during sorafenib administration with a frequent performance of liver function tests and clinicians should consider sorafenib dose modification to minimize sorafenib-induced liver injury.

Most HCC patients have underlying liver cirrhosis; therefore, hepatic reserve is a high priority in selecting HCC treatment strategies and is strongly associated with post-treatment complications [4, 28]. Thus, extensive efforts have been made to assess hepatic functional reserve. For instance, indocyanine green retention rate at 15 min (ICG 15) has been widely used to assess preoperative hepatic reserve and predict post-hepatectomy liver failure especially in Asian countries [29, 30]. Recently, Lee et al [31] identified MRE-assessed LS as a more potent biomarker for predicting post-hepatectomy liver failure than ICG 15 and other traditional serum markers. Additionally, MRE-assessed LS was negatively correlated with postoperative hepatic regeneration [32]. These findings suggest that LS measured by MRE is a potent biomarker to assess underlying hepatic reserve by reflecting the degree of hepatic fibrosis that restricts the hepatic reserve. Similarly, in our study, MRE-assessed LS was identified as a strong predictor of severe liver injury after sorafenib administration. Majority of sorafenib-induced liver injury is known to be idiosyncratic hepatotoxicity [10], which seems to occur as a transient and mild event that most patients with adequate hepatic reserve and endurance recover from. However, hepatic failure occurs more frequently in patients with insufficient hepatic reserve who cannot endure even minimal hepatocellular damage.

In this study, MRE-assessed LS was significantly correlated with serum bilirubin and albumin, which are assessment components of the Child-Pugh score, the most widely used scoring system for assessing hepatic reserve in clinical practice. Interestingly, MRE-assessed LS demonstrated a much more potent power for predicting OS and severe liver injury than that of the Child-Pugh score or traditional serum markers such as albumin or bilirubin. These results suggest that MRE-assessed LS can predict hepatic reserve more accurately than traditional serum marker-based models. MRE can be easily integrated into routine MRI



**Fig. 5** Correlation between liver stiffness (LS) assessed using magnetic resonance elastography (MRE) and clinical variables (**a** albumin and **b** total bilirubin)

protocols, and the clinical use of this attractive image-based biomarker would be relatively convenient. In the future, active use of MRE-assessed LS could contribute to developing precision medicine strategies for HCC, which would improve the prognosis of HCC patients.

A major challenge in cancer treatment is predicting therapeutic response to anticancer drugs on a precision basis. MRE has shown a future role in precision medicine for HCC by demonstrating that MRE-assessed tumor stiffness is associated with histopathology feature and treatment response to pembrolizumab [33, 34]. The result seems promising especially in advanced HCC patients with limited options for treatment and whose hepatic parenchyma has been completely replaced by the tumor. In the present study, MRE-assessed LS, but not tumor stiffness, was evaluated as a prognostic marker in sorafenib-treated HCC. Because LS reflected hepatic functional reserve, but not tumor characteristics, it was a significant predictor of OS, but not associated with PFS. With this, further studies investigating the potential association between MRE-assessed tumor stiffness and therapeutic effect of anticancer drug along with PFS or even OS would be an interesting research focus.

Our study has a few limitations. First, there was a possible selection bias because of the retrospective study design. Specifically, a considerable number of patients who did not undergo liver MRI and missed MRE were excluded from the analysis. Second, although we obtained significant results, a relatively small number of patients were included in the study; therefore, further studies with a larger number of patients are warranted. Third, MRE was acquired across field strengths, which may potentially have affected the LS values. However, because LS measurement was shown to be highly reproducible across field strengths, we believe it would have little effect on the results [17, 35]. Finally, the measurement was performed by one reader, which might limit the transferability. However, high inter-reader agreement for LS by MRE was previously reported [17, 35].

Thus, we confirmed the clinical feasibility of applying MRE-assessed LS in predicting the prognosis of advanced HCC patients treated with sorafenib. A high MRE-assessed LS is a predictor of poor OS and is associated with the development of sorafenib-induced significant liver injury. Proactive use of MRE-assessed LS as a prognostic predictor in pretreatment assessment would facilitate the planning of personalized therapeutic strategies for advanced HCC patients.

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### Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Hyo Jung Cho.

**Conflict of interest** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Statistics and biometry** Hyo Jung Cho performed the statistical analysis.

**Informed consent** The requirement for written informed consent was waived by the institutional review board.

**Ethical approval** Institutional review board approval of Ajou University Hospital was obtained.

### Methodology

- Retrospective
- Diagnostic or prognostic study
- Single-center study

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