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Validation and expansion of Baveno VII criteria for cACLD and CSPH based on liver stiffness and platelet count: Correlation with risk of hepatic decompensation and death

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Abstract

Background and Aims: Recently proposed "Rule-of-Five" criteria define compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH) using liver stiffness (LS) and platelet

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALD, alcohol-associated liver disease; BMI, body mass index; cACLD, compensated advanced chronic liver disease; CDW, corporate data warehouse; CSPH, clinically significant portal hypertension; EASL, European Association for the Study of the Liver; ICD, International Classification of Diseases; LS, liver stiffness; MASLD, metabolic dysfunction–associated steatotic liver disease; VCTE, vibration-controlled transient elastography; VHA, Veterans Health Administration.

Philip Vutien and Abbey Barnard Giustini are primary co-authors.

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count. We aimed to validate these criteria by determining whether they are associated with risk of adverse outcomes.

Approach and Results: Patients without prior hepatic decompensation or HCC who underwent LS and platelet measurements (n = 17,076) were categorized as follows: no cACLD (LS: 2.5–9.9 kPa); probable cACLD (LS: 10–14.9 kPa); certain cACLD-no CSPH (LS: 15–19.9 kPa and platelets ≥110,000/μL or LS 20–24.9 kPa and platelets ≥150,000/μL); probable CSPH (LS 15–19.9 kPa and platelets <110,000/μL or LS 20–24.9 and platelets <150,000/μL); and certain CSPH (LS ≥25 kPa), which we further subdivided into 25–49.9 and 50–75 kPa. During a median follow-up of 2.82 years, each increase in the "Rule-of-Five" category was associated linearly with higher risks of death (HR: 1.22, 95% CI: 1.18–1.25) and decompensation (HR: 1.52, 95% CI: 1.46–1.58). Compared to patients with LS 25–49.9 kPa, those with LS 50–75 kPa ("critical" CSPH) had approximately double the risk of decompensation (11.24 vs. 4.20 per 100 patient-years) and death (9.85 vs. 6.98 per 100 patient-years).

Conclusions: The Baveno VII "Rule-of-Five" criteria provide a valid system for stratifying risks of death and hepatic decompensation and should be used routinely in patients with chronic liver disease. Among patients with CSPH (LS ≥25 kPa), the subgroup with LS 50–75 kPa ("critical" CSPH) has approximately double the risk of death and hepatic decompensation than LS 25–49.9 kPa.

Keywords: HCC, hepatic decompensation, transient elastography

INTRODUCTION

Progression of chronic liver disease can lead to cirrhosis, complications of portal hypertension, HCC, and death.[1] Chronic HCV, chronic HBV, alcohol-associated liver disease (ALD), and metabolic dysfunction–associated steatotic liver disease (MASLD) account for the vast majority of chronic liver disease, and rates of both MASLD and ALD continue to rise.[2,3]

Although vibration-controlled transient elastography (VCTE)-derived liver stiffness (LS) is a commonly used noninvasive test of liver fibrosis, it also correlates well with portal pressure. Higher LS values have been associated with an increased risk of portal hypertensive complications (ie, ascites, variceal bleeding, and HE) and HCC.[4,5] Pons and colleagues initially proposed using LS and platelet counts to stratify the risk of compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH). This noninvasive approach, called the "Rule-of-Five", suggests that cACLD can be excluded when LS is <10 kPa and that CSPH can be excluded when LS is <15 kPa and platelet count is >150,000/μL. CSPH is assumed when LS exceeds 25 kPa. Finally, probable CSPH (a minimum risk of at least 60%) is defined by (1) LS 15–20 kPa and platelet count <110,000/μL or (2) LS 20–25 kPa and platelet count <150,000/μL. The "Rule-of-Five" approach has since been validated in diverse clinical settings[6–8] and has been adapted by the Baveno workshop, the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD).[9–12]

We aimed to validate the Baveno "Rule-of-Five" system by determining whether increasing categories are associated with increasing risk of complications of portal hypertension, including among patients with obesity and MASLD in whom LS ≥25 kPa has a much lower positive predictive value for HVPG ≥10 mm Hg than in other liver diseases.[13] In addition, we wanted to determine if these categories are also associated with risks of HCC and all-cause mortality. Finally, we wanted to investigate among patients who have LS ≥25 kPa and are defined as having "certain CSPH," whether increasing LS values beyond 25 kPa (eg, 50–75 vs. 25–49.9 kPa) are associated with higher risks of mortality, decompensation, and HCC.

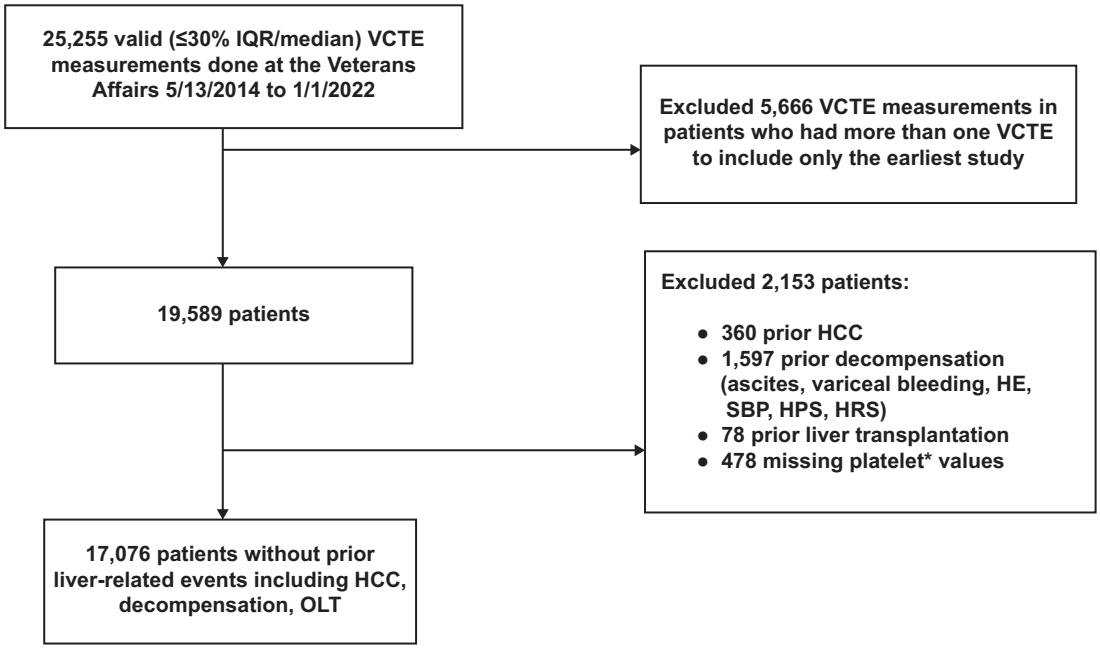


FIGURE 1 Derivation of the final analytic cohort of 17,076 patients with valid Fibroscan-derived LS measurements. *Missing recent (within 6 mo before LS date) platelet values for those who had baseline liver stiffness measurements between 15 and 24.9 kPa. Abbreviations: HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; LS, liver stiffness; SBP, spontaneous bacterial peritonitis; VCTE, vibration-controlled transient elastography.

METHODS

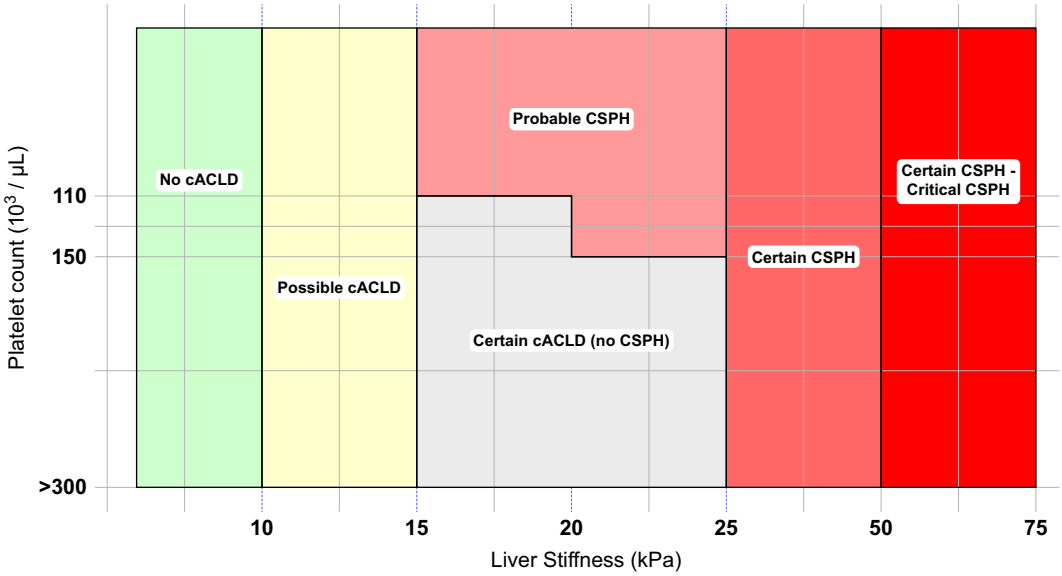
Study design and study population

We created a retrospective cohort of US Veterans who underwent LS measurements in the Veterans Health Administration (VHA) from May 13, 2014, to January 1, 2022. The VHA is the largest integrated health care system in the United States, serving more than 7 million Veterans each year through its 168 VA Medical Centers and 1053 outpatient clinics. The corporate data warehouse (CDW) is a national and continually updated repository of VHA electronic health records.

Using data from CDW, we identified a total of 19,589 patients who underwent 25,255 valid VCTE measurements (defined as having an IQR divided by median LS measurement of $\leq 30\%$[14]) conducted at the VHA. Among those patients with multiple VCTEs, we included only the earliest measurement. We excluded patients who had documentation of the following events before LS measurement: hepatic decompensation (ascites, bleeding gastro-esophageal varices, HE, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatopulmonary syndrome; n = 1597), HCC (n = 360), or liver transplantation (n = 78). We also excluded patients with LS between 15 and 24.9 kPa who did not have platelet values within 6 months of LS measurement (n = 478), since their "Rule-of-Five" category could not be determined. Our final analytic cohort consisted of 17,076 patients who were retrospectively followed from the time of LS measurement until January 1, 2022, for death, hepatic decompensation (including gastro-esophageal variceal bleeding alone), and HCC (Figure 1).

Baseline patient characteristics

We ascertained age, body mass index (BMI), and baseline laboratory values within 6 months and before the LS date. We determined the presence of type 2 diabetes mellitus and alcohol use disorder based on appropriate International Classification of Diseases (ICD)-9 revision and ICD-10 codes recorded at least twice in any inpatient or outpatient encounter before the date of LS measurement (Supplemental Table S1, http://links.lww.com/HEP/J642). The patients' underlying chronic liver diseases were categorized according to a hierarchical approach that has been used by us and other investigators (Supplemental Table S2, http://links.lww.com/HEP/J642).[15,16] We also collected recent use of nonselective beta-blockers, defined as the prescription fill of carvedilol, propranolol, or nadolol within 90 days of VCTE.



Liver Stiffness (kPa)	Platelet Count (per µL)	Baveno VII "Rule of Five" Classification
<10	Any	No cACLD
10-14.9	Any	Probable cACLD
15-19.9	≥110,000	Certain cACLD (no CSPH)
20-24.9	≥150,000	Certain cACLD (no CSPH)
15-19.9	<110,000	Probable CSPH
20-24.9	<150,000	Probable CSPH
25-49.9	Any	Certain CSPH
50-75	Any	Certain CSPH-Critical CSPH*

"Critical CSPH" is a subgroup of CSPH that we investigated by taking the upper half of the range of LS for CSPH

FIGURE 2 The proposed Baveno VII and EASL/AASLD "Rule-of-Five" categories determined by liver stiffness and platelet thresholds to indicate cACLD and CSPH. We categorized patients according to incremental categories proposed by the Baveno VII workshop and adopted by EASL and AASLD guidelines, which include, in terms of increasing risk of portal hypertensive complications, no cACLD, probable cACLD, certain cACLD-no CSPH, probable CSPH, and certain CSPH. We subcategorized those with certain CSPH (LS ≥25 kPa) into LS 25–49.9 kPa and LS ≥50 kPa, which we labeled as "critical CSPH," to capture excess risk of hepatic decompensation and death. Abbreviations: AASLD, American Association for the Study of Liver Diseases; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; EASL, European Association for the Study of the Liver; LS, liver stiffness.

Determination of Baveno "Rule-of-Five" categories of cACLD and CSPH using LS and platelet counts

We used LS and platelet values within 6 months before LS measurement to categorize patients according to the Baveno VII and AASLD "Rule-of-Five" criteria as shown in Figure 2, into the following incremental categories: no cACLD, probable cACLD, certain cACLD-no CSPH, probable CSPH, and certain CSPH.[9,10] To investigate whether the category of certain CSPH (LS: 25–75 kPa) can be further subdivided in a meaningful way that correlates with the risk of decompensation, we divided patients into 2 categories of equal LS range, that is, 25–49.9 kPa and 50–75 kPa, the latter of which we labeled "critical CSPH."

Outcomes: mortality, hepatic decompensation, and HCC

We evaluated the association between LS-platelet risk categories and time to the following outcomes:

(1) All-cause mortality is defined as death due to any etiology using data from the CDW. The CDW includes data on deaths from a variety of sources, including VA inpatient files, VA Beneficiary Identification and Records Locator System, Social Security Administration, death files, and the Department of Defense.[17]
(2) Hepatic decompensation is defined by the development of new ascites, HE, bleeding gastro-esophageal varices, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatopulmonary

TABLE 1 Baseline characteristics of 17,076 patients without prior hepatic decompensation, HCC, or liver transplantation and with a valid Fibroscan liver stiffness measurement, stratified by Baveno VII "Rule-of-Five" categories of cACLD and CSPH

Rule-of-five description	All patients	No cACLD	Probable cACLD	Certain cACLD, no CSPH		Probable CSPH	Certain CSPH	Critical CSPH
Liver stiffness, kPa	NA	2.5–9.9	10–14.9	15–19.9	20–24.9	15–24.9	25–49.9	50–75
Platelet count, /μL	NA	NA	NA	≥ 110,000	≥ 150,000	< 110,000 or < 150,000	NA	NA
Number	N = 17,076	n = 9305	n = 3437	n = 1279	n = 582	n = 529	n = 1457	n = 487
Age, median, y (IQR)	64.6 (59.1–69.7)	64.5 (58.5–69.8)	65.2 (60.3–69.8)	64.8 (59.4–70.0)	64.9 (59.4–69.4)	65.1 (60.5–70.5)	63.7 (59.0–68.8)	63.7 (58.3–69.2)
Male, n (%)	16,323 (95.6)	8844 (95.1)	3317 (96.5)	1222 (95.5)	553 (95.0)	511 (96.6)	1404 (96.4)	472 (96.9)
Race/ethnicity, n (%)								
Non-Hispanic White	8997 (52.7)	4450 (47.8)	1879 (55.7)	774 (60.5)	349 (60.0)	342 (64.7)	893 (61.3)	310 (63.7)
Non-Hispanic Black	5463 (32.0)	3357 (36.1)	1067 (31.0)	340 (26.6)	149 (25.6)	107 (20.2)	329 (22.6)	114 (23.4)
Asian	443 (2.6)	369 (4.0)	46 (1.3)	6 (0.5)	7 (1.2)	4 (0.8)	8 (0.6)	3 (0.6)
Hispanic	1065 (6.2)	545 (5.9)	222 (6.5)	77 (6.0)	37 (6.4)	40 (7.6)	118 (8.1)	26 (5.3)
Other	821 (4.8)	437 (4.7)	158 (4.6)	61 (4.8)	25 (4.3)	28 (5.3)	83 (5.7)	29 (6.0)
Missing	287 (1.7)	147 (1.6)	65 (1.9)	21 (1.6)	15 (2.6)	8 (1.5)	26 (1.8)	5 (1.0)
Liver disease etiology, n (%)								
Active HCV	5768 (33.8)	2784 (29.9)	1401 (40.8)	448 (35.0)	194 (33.3)	212 (40.1)	577 (39.6)	152 (31.2)
Cured HCV	2743 (16.1)	1800 (19.3)	524 (15.3)	157 (12.3)	59 (10.1)	40 (7.6)	134 (9.2)	29 (6.0)
Chronic HBV	1431 (8.4)	1233 (13.3)	122 (3.6)	26 (2.0)	9 (1.6)	13 (2.5)	23 (1.6)	5 (1.0)
MASLD	3739 (21.9)	1677 (18.0)	813 (23.7)	392 (30.7)	198 (34.0)	149 (16.5)	385 (26.4)	125 (25.7)
Alcohol-associated	1783 (10.4)	660 (7.1)	358 (10.4)	176 (13.8)	87 (15.0)	87 (16.5)	259 (17.8)	156 (32.0)
Cryptogenic	1069 (6.3)	788 (8.5)	137 (4.0)	46 (3.6)	22 (3.8)	16 (3.0)	46 (3.2)	14 (2.9)
Other	543 (3.2)	363 (3.9)	82 (2.4)	34 (2.7)	13 (2.2)	12 (2.3)	33 (2.3)	6 (1.2)
Comorbidities, n (%)								
Diabetes	6916 (40.5)	3173 (34.1)	1545 (45.0)	649 (50.7)	312 (53.6)	272 (51.4)	728 (50.0)	237 (48.7)
Hypertension	10,956 (64.2)	5824 (62.6)	2257 (65.7)	847 (66.2)	396 (68.0)	346 (65.4)	956 (65.6)	330 (67.8)
Alcohol use disorder	10,321 (60.4)	5599 (60.2)	2038 (59.3)	763 (59.7)	346 (59.5)	304 (57.5)	923 (63.4)	348 (71.5)
BMI, median, kg/m^2 (IQR)	29.0 (25.3–33.2)	28.3 (42.9–32.1)	29.4 (25.6–33.9)	30.5 (26.2–35.0)	31.4 (26.8–36.9)	29.5 (25.7–33.9)	30.2 (26.1–35.0)	31.1 (26.8–35.6)
AST, median, U/L (IQR)	32 (23–53)	27 (20–38)	38 (26–61)	44 (29–71)	44 (29–69)	50 (31–82)	57 (36–93)	58.5 (38–92)
ALT, median, U/L (IQR)	35 (22–60)	28 (19–46)	42 (25–72)	48 (28–78)	49 (30–79)	47 (28–88)	53 (32–89)	42 (26–68)

Abbreviations: BMI, body mass index; cACLD, compensated advanced liver disease; CSPH, clinically significant portal hypertension; MASLD, metabolic dysfunction–associated steatotic liver disease.

syndrome. Whichever of these conditions developed first was taken as the first decompensating event. As almost all patients who undergo liver transplantation will have experienced prior hepatic decompensation, we included liver transplant as a "decompensating" event. The development of each of these conditions was based on appropriate ICD-9, ICD-10, or Current Procedural Terminology codes recorded at least twice. This approach has been validated and widely used in VA-based studies by our group and others.[16,18–26] In addition, HE was defined by the prescription of lactulose, rifaximin, or neomycin for more than 90 days.[27]

(3) Gastro-esophageal variceal bleeding alone was defined by the presence of appropriate ICD-9 and ICD-10 codes recorded at least once, as our group

TABLE 2 Association between Baveno VII "Rule-of-Five" categories of cACLD and CSPH and risk of mortality, hepatic decompensation, variceal bleeding, and HCC

	Risk group	Number of patients	Patient-years	Number with outcome	Incidence (per 100 patient-years)	HR (95% CI)	Adjusted HR[a] (95% CI)	HR per increase in "Rule-of-Five"[b] category
	A. Mortality							1.30 (1.25–1.35)
No cACLD	LS 2.5–9.9	9305	25,806	889	3.44	0.90 (0.80–1.02)	0.90 (0.80–1.01)	
Probable cACLD	LS 10–14.9	3437	10,618	413	3.89	Reference	Reference	
Certain cACLD, no CSPH	LS 15–19.9 and platelets ≥110,000	1279	3680	157	4.27	1.11 (0.92–1.33)	1.17 (0.97–1.40)	
	LS 20–24.9 and platelets ≥150,000	582	1698	74	4.36	1.13 (0.88–1.45)	1.24 (0.96–1.59)	
Probable CSPH	LS 15–19.9 and platelets <110,000 or LS 20–24.9 and platelets <150,000	529	1591	88	5.53	1.43 (1.14–1.80)	1.38 (1.09–1.74)	
Certain CSPH	LS 25–49.9	1457	4500	314	6.98	1.80 (1.56–2.09)	1.85 (1.59–2.15)	
Critical CSPH	LS 50–75	487	1391	137	9.85	2.58 (2.13–3.13)	2.73 (2.24–3.33)	
	B. Hepatic decompensation							1.77 (1.68–1.87)
No cACLD	LS 2.5–9.9	9305	25,409	279	1.10	0.77 (0.63–0.94)	0.84 (0.69–1.04)	
Probable cACLD	LS 10–14.9	3437	10,397	146	1.40	Reference	Reference	
Certain cACLD, no CSPH	LS 15–19.9 and platelets ≥110,000	1279	3603	52	1.44	1.02 (0.74–1.40)	0.97 (0.70–1.33)	
	LS 20–24.9 and platelets ≥150,000	582	1654	35	2.12	1.54 (1.06–2.23)	1.40 (0.96–2.04)	
Probable CSPH	LS 15–19.9 and platelets <110,000 or LS 20–24.9 and platelets <150,000	529	1526	48	3.15	2.23 (1.61 – 3.09)	2.02 (1.45–2.80)	
Certain CSPH	LS 25–49.9	1457	4211	177	4.20	2.98 (2.40–3.71)	2.75 (2.20–3.43)	
Critical CSPH	LS 50–75	487	1193	134	11.24	7.87 (6.23–9.95)	6.56 (5.15–8.36)	
	C. Gastro-esophageal variceal bleeding							2.29 (2.00–2.63)
No cACLD	LS 2.5–9.9	9305	25,764	29	0.11	0.62 (0.35–1.10)	0.61 (0.34–1.10)	
Probable cACLD	LS 10–14.9	3437	10,589	19	0.18	Reference	Reference	
Certain cACLD, no CSPH	LS 15–19.9 and platelets ≥110,000	1279	3665	10	0.27	1.51 (0.70–3.25)	1.43 (0.67–3.09)	
	LS 20–24.9 and platelets ≥150,000	582	1683	7	0.42	2.30 (0.97–5.47)	2.09 (0.87–4.98)	
Probable CSPH	LS 15–19.9 and platelets <110,000 or LS 20–24.9 and platelets <150,000	529	1568	14	0.89	4.95 (2.48–9.87)	4.50 (2.25–9.00)	

TABLE 2. (*continued*)

	Risk group	Number of patients	Patient-years	Number with outcome	Incidence (per 100 patient-years)	HR (95% CI)	Adjusted HR[a] (95% CI)	HR per increase in "Rule-of-Five"[b] category
Certain CSPH	LS 25–49.9	1457	4427	42	0.95	5.27 (3.07–9.06)	4.47 (2.59–7.72)	
Critical CSPH	LS 50–75	487	1349	28	2.08	11.43 (6.38–20.47)	8.39 (4.61–15.28)	
	D. Hepatocellular carcinoma							1.47 (1.38–1.57)
No cACLD	LS 2.5–9.9	9305	25,429	212	0.83	0.56 (0.45–0.68)	0.62 (0.50–0.77)	
Probable cACLD	LS 10–14.9	3437	10,332	154	1.49	Reference	Reference	
Certain cACLD, no CSPH	LS 15–19.9 and platelets ≥ 110,000	1279	3592	46	1.28	0.85 (0.61–1.19)	0.94 (0.67–1.31)	
	LS 20–24.9 and platelets ≥ 150,000	582	1648	31	1.88	1.25 (0.85–1.85)	1.51 (1.02–2.22)	
Probable CSPH	LS 15–19.9 and platelets < 110,000 or LS 20–24.9 and platelets < 150,000	529	1523	37	2.43	1.63 (1.14–2.33)	1.69 (1.18–2.44)	
Certain CSPH	LS 25–49.9	1457	4284	118	2.75	1.85 (1.45–2.35)	2.06 (1.60–2.63)	
Critical CSPH	LS 50–75	487	1344	30	2.23	1.49 (1.01–2.20)	1.97 (1.32–2.95)	
	E. Composite outcome (mortality, hepatic decompensation, or HCC)							1.40 (1.36–1.45)
No cACLD	LS 2.5–9.9	9305	25,043	1218	4.86	0.82 (0.74–0.90)	0.84 (0.76–0.93)	
Probable cACLD	LS 10–14.9	3437	10,126	605	5.97	Reference	Reference	
Certain cACLD, no CSPH	LS 15–19.9 and platelets ≥ 110,000	1279	3520	215	6.11	1.02 (0.88–1.19)	1.06 (0.90–1.24)	
	LS 20–24.9 and platelets ≥ 150,000	582	1609	115	7.15	1.20 (0.98–1.46)	1.29 (1.06–1.59)	
Probable CSPH	LS 15–19.9 and platelets < 110,000 or LS 20–24.9 and platelets < 150,000	529	1464	135	9.22	1.55 (1.28–1.86)	1.49 (1.23–1.80)	
Certain CSPH	LS 25–49.9	1457	4035	470	11.65	1.95 (1.73–2.20)	1.99 (1.75–2.25)	
Critical CSPH	LS 50–75	487	1154	222	19.24	3.22 (2.76–3.76)	3.28 (2.79–3.84)	

[a]Adjusted for baseline age, sex, race/ethnicity, BMI, diabetes, Charlson comorbidity index, etiology of liver disease, and history of alcohol use.
[b]When categorized according to these "Rule of Five" risk categories: (1) LS 2.5–9.9 kPa; (2) LS 10–14.9 kPa; (3) LS 15–19.9 kPa and platelets < 110,000/μL or LS 20–24.9 and platelets < 150,000/μL; and (4) LS > 25 kPa.
Abbreviations: BMI, body mass index; cACLD, compensated advanced liver disease; CSPH, clinically significant portal hypertension; LS, liver stiffness.

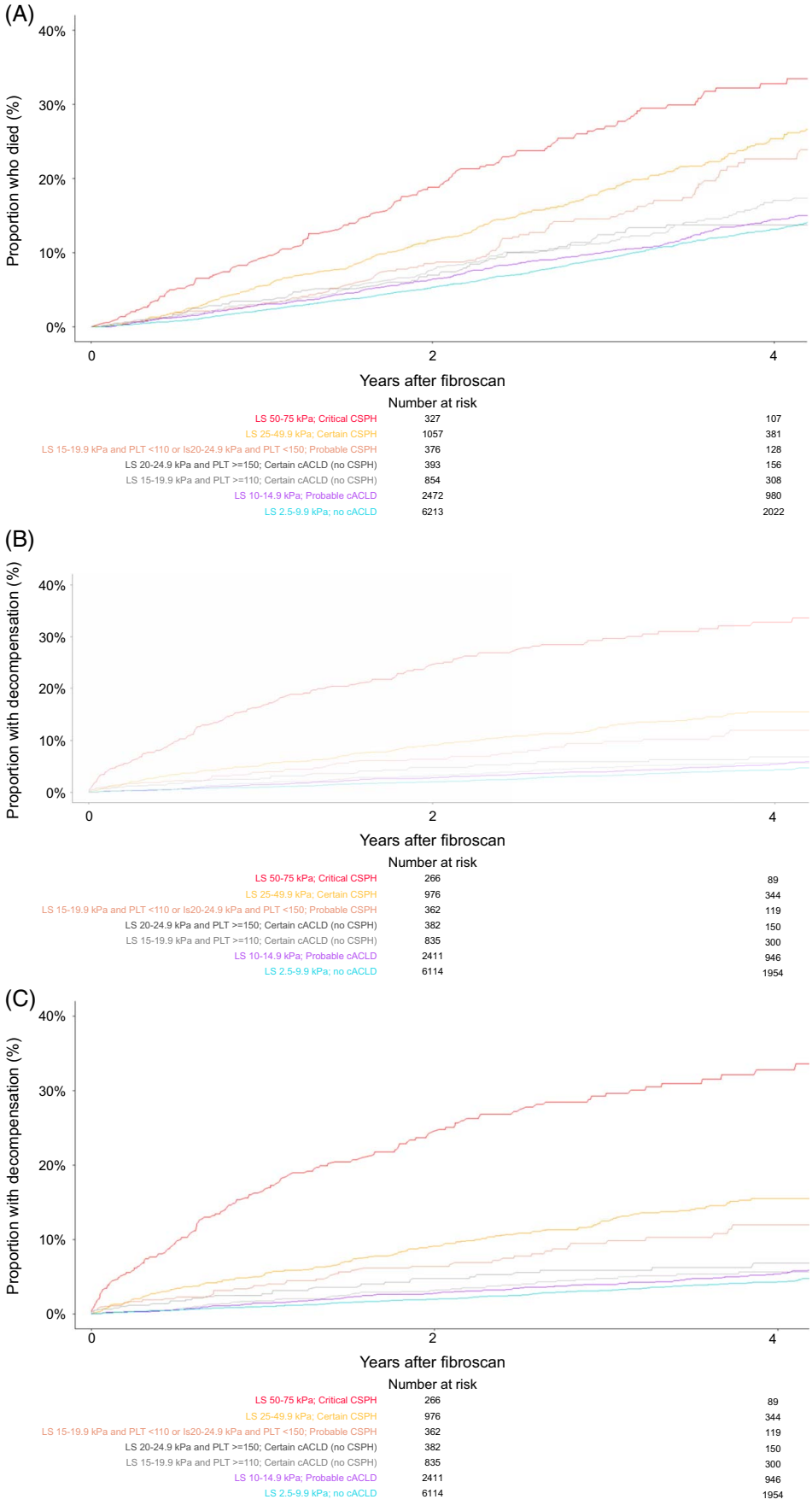

(A)
Proportion who died (%)
40%
30%
20%
10%
0%
0
2
4
Years after fibroscan
Number at risk
LS 50-75 kPa; Critical CSPH 327 107
LS 25-49.9 kPa; Certain CSPH 1057 381
LS 15-19.9 kPa and PLT <110 or ls20-24.9 kPa and PLT <150; Probable CSPH 376 128
LS 20-24.9 kPa and PLT >=150; Certain cACLD (no CSPH) 393 156
LS 15-19.9 kPa and PLT >=110; Certain cACLD (no CSPH) 854 308
LS 10-14.9 kPa; Probable cACLD 2472 980
LS 2.5-9.9 kPa; no cACLD 6213 2022
(B)
Proportion with decompensation (%)
40%
30%
20%
10%
0%
0
2
4
Years after fibroscan
Number at risk
LS 50-75 kPa; Critical CSPH 266 89
LS 25-49.9 kPa; Certain CSPH 976 344
LS 15-19.9 kPa and PLT <110 or ls20-24.9 kPa and PLT <150; Probable CSPH 362 119
LS 20-24.9 kPa and PLT >=150; Certain cACLD (no CSPH) 382 150
LS 15-19.9 kPa and PLT >=110; Certain cACLD (no CSPH) 835 300
LS 10-14.9 kPa; Probable cACLD 2411 946
LS 2.5-9.9 kPa; no cACLD 6114 1954
(C)
Proportion with decompensation (%)
40%
30%
20%
10%
0%
0
2
4
Years after fibroscan
Number at risk
LS 50-75 kPa; Critical CSPH 266 89
LS 25-49.9 kPa; Certain CSPH 976 344
LS 15-19.9 kPa and PLT <110 or ls20-24.9 kPa and PLT <150; Probable CSPH 362 119
LS 20-24.9 kPa and PLT >=150; Certain cACLD (no CSPH) 382 150
LS 15-19.9 kPa and PLT >=110; Certain cACLD (no CSPH) 835 300
LS 10-14.9 kPa; Probable cACLD 2411 946
LS 2.5-9.9 kPa; no cACLD 6114 1954

FIGURE 3 Kaplan-Meier cumulative incidence curves, according to Baveno VII Rule-of-Five risk category, of (A) mortality, (B) decompensation, (C) gastro-esophageal variceal bleeding, (D) HCC, and (E) composite outcome (death, decompensation, or HCC). The incidence of mortality, decompensation, gastro-esophageal variceal bleeding, and the composite outcome increased linearly with each incremental Baveno "Rule-of-Five" category. HCC risk peaked at LS 25–50 kPa and did not increase for the LS 50–75 kPa category. Abbreviation: LS, liver stiffness.

has done in prior studies.[28] A single recording was required for bleeding varices because many patients may experience only a single bleeding episode.

(4) HCC, which was ascertained from ICD-9 code 155.0 or ICD-10 code C22.0, was recorded at least twice. The ICD codes documented in VA records have been shown to have a positive predictive value of 84%–94% compared to chart extraction and have been widely used by our group and other investigators.[18,29]

(5) A composite outcome, which was defined by all-cause death, hepatic decompensation, or HCC, whichever occurred first.

Statistical analyses

Patients were followed from the date of LS measurement (time zero) until January 1, 2022, for the development of the 4 outcomes of interest (ie, mortality, decompensation, variceal bleeding, or HCC). "Rule-of-Five" categories were examined both categorically and as incremental categories. For the outcomes of decompensation (including variceal bleeding) and HCC, patients were censored at the end of follow-up on January 1, 2022, or at the time of death, whichever occurred first. When evaluating the risk of HCC, patients who experienced hepatic decompensation were not censored at the time of decompensation, as they remain at risk for developing HCC. Similarly, when assessing the risk of hepatic decompensation, patients who were diagnosed with HCC were not censored at this date, as these patients continue to be at risk for decompensation. Incidence per 100 patient-years was calculated for each outcome. Unadjusted (crude) and adjusted multivariable Cox proportional hazards regression was used to assess for associations between risk categories and each of the 5 outcomes. We decided a priori to include in our multivariable models the following baseline characteristics and potential confounders: age, sex, race/ethnicity, BMI, diabetes, Charlson comorbidity index, etiology of liver disease, and history of alcohol use disorder. These are patient characteristics that have been previously demonstrated to be associated with mortality, decompensation, or HCC and thus may be confounding any association between "Rule-of-Five" categories and these outcomes.[28,30–35]

We performed the following sensitivity and subgroup analyses to assess the robustness of our results. First, we used the Fine-Gray method to conduct a competing risks analysis accounting for the competing risks of death when evaluating the outcomes of hepatic decompensation or HCC.[36] Second, we performed subgroup analyses for patients with MASLD or patients with MASLD and obesity (ie, BMI >30 kg/m^2) because LS does not correlate as well with CSPH (as diagnosed by HVPG ≥ 10 mm Hg) in patients with MASLD and obesity as it does in other liver disease etiologies.[13,37] Third, we performed a subgroup analysis excluding patients who had active HCV at baseline, given that active HCV is declining as an etiology for chronic liver disease. Fourth, because patients with active HCV at baseline may undergo antiviral treatment and achieve sustained virologic response during follow-up, which is expected to reduce their risk of adverse outcomes, we performed a sensitivity analysis in which we censored patients with active HCV at the time they achieved sustained virologic response during follow-up, if applicable.

All analyses were performed in RStudio (version 2023.12.1+402).

All research was conducted in accordance with the Declarations of Helsinki and Istanbul, approved by the Institutional Review Board of Veterans Affairs Puget Sound Health Care System, which granted a waiver of informed consent.

RESULTS

Baseline characteristics of the study cohort

Our cohort consisted of 17,076 US Veterans who were predominantly male (95.6%) and racially and ethnically diverse (52.7% non-Hispanic White, 32.0% non-Hispanic Black, and 6.2% Hispanic), with a median age of 66.5 years (IQR: 60.2–71.3 y) (Table 1). Diabetes (40.5%), hypertension (64.2%), and a history of alcohol use disorder (60.4%) were common comorbidities. The most common etiologies of liver disease were HCV (49.9%, including active HCV in 33.8% and cured HCV in 16.1%), MASLD (21.9%), or ALD (10.4%). When stratified by the "Rule-of-Five" risk categories of cACLD and CSPH, patients in higher-risk groups were more likely to be White and have ALD and diabetes, while less likely to be Black and have cured HCV, compared to patients in lower-risk groups (Table 1).

Associations between Baveno "Rule-of-Five" categories and mortality risk

Over a median follow-up time of 2.82 years (IQR: 1.48–3.94 y), 2072 (12.1%) patients died (Table 2 and

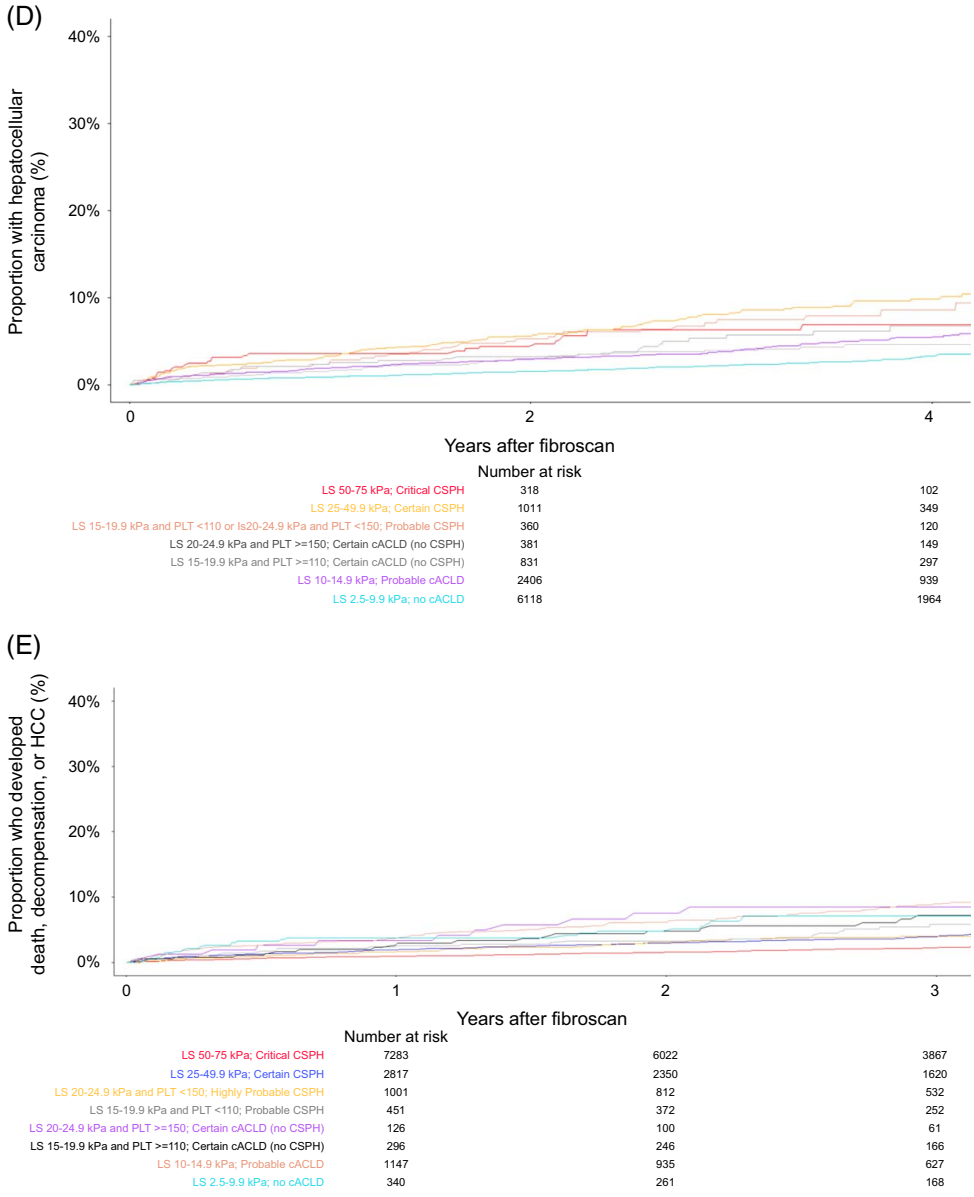


FIGURE 3 *(Continued).*

Figure 3A). Mortality increased with each incremental "Rule-of-Five" category (Figure 4) from no cACLD (3.44 per 100 patient-years), to probable cACLD (3.89 per 100 patient-years), certain cACLD-no CSPH (4.27–4.36 per 100 patient-years), and to probable CSPH (5.53 per 100 patient-years). The mortality rate continued to increase for those with certain CSPH who had LS values beyond 25 kPa: those with LS 25–49.9 kPa experienced a mortality rate of 6.98 per 100 patient-years, which increased to 9.85 per 100 patient-years for those with LS 50–75 kPa ("critical CSPH"). Each increase in the "Rule-of-Five" category was also associated with a 30% (95% CI: 25%–35%) increased risk of mortality (HR: 1.30, 95% CI: 1.25–1.35) (Table 2). An increase of 5 kPa in LS beyond 25 kPa was associated with a 5% increased risk of death (95% CI: 3%–8%).

Associations between Baveno "Rule-of-Five" categories and hepatic decompensation and variceal bleeding risk

During a median follow-up time of 2.75 years (IQR: 1.34–3.89 y), 871 patients (5.1%) experienced a hepatic decompensation event (Table 2 and Figure 3B), of whom 149 (0.8% of the total population) had new variceal bleeding (Figure 3C). The risk of hepatic decompensation increased with each incremental "Rule-of-Five" category (Figure 4), from no cACLD (1.10 per 100 patient-years), to probable cACLD (1.40 per 100 patient-years), certain cACLD-no CSPH (1.44–2.12 per 100 patient-years), and to probable CSPH (3.15 per 100 patient-years). The risk of decompensation and variceal bleeding continued to increase for those with certain CSPH with LS values beyond 25 kPa. Those with LS 25–49.9 kPa experienced a

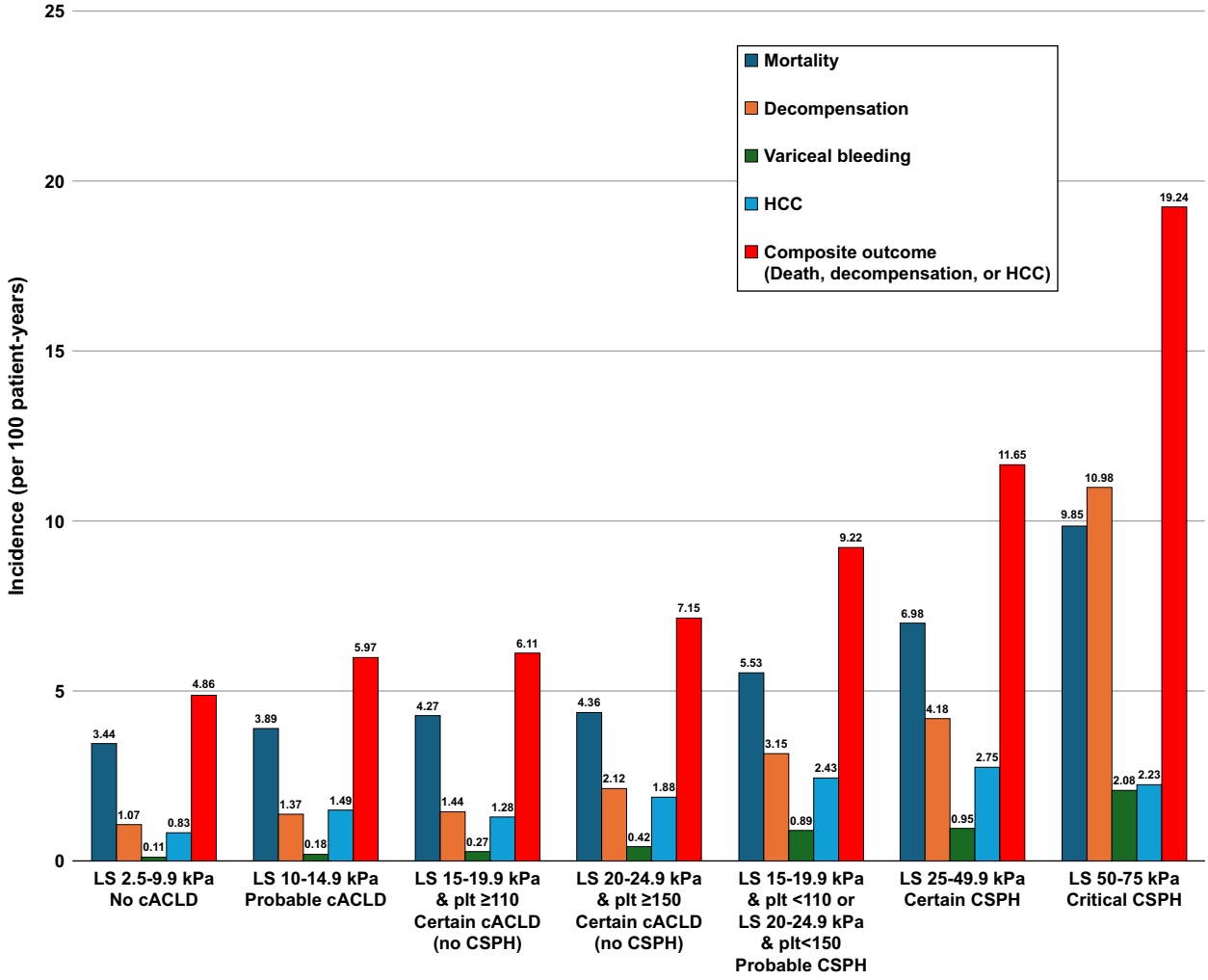


FIGURE 4 Incidence of mortality, decompensation, variceal bleeding, HCC, and the composite outcome when stratified by "Rule-of-Five" risk categories. The incidence of mortality, decompensation, and gastro-esophageal variceal bleeding, and the composite outcome increased linearly with each incremental Baveno "Rule-of-Five" category. HCC risk peaked at LS 25–50 kPa and did not increase for the LS 50–75 kPa category. Abbreviation: LS, liver stiffness.

hepatic decompensation risk of 4.20 per 100 patient-years and a variceal bleeding risk of 0.95 per 100 patient-years. Risks of hepatic decompensation and variceal bleeding increased to 11.24 and 2.08 per 100 patient-years, respectively, for those with LS 50–75 kPa ("critical CSPH"). Each increase in the "Rule-of-Five" risk category was associated with a 77% (95% CI: 68%–87%) increased risk of decompensation (HR: 1.77, 95% CI: 1.68–1.87) and a 129% (95% CI: 100%–163%) increased risk of variceal bleeding (HR: 2.29, 95% CI: 2.00–2.63). For every 5 kPa increase beyond 25 kPa, the risk of decompensation increased by 14% (95% CI: 10%–17%), and the risk of variceal bleeding increased by 11% (95% CI: 4%–18%).

Associations between Baveno "Rule-of-Five" categories and HCC risk

During a median follow-up time of 2.77 years (IQR: 1.35–3.90 y), 628 patients (3.7%) developed HCC (Table 2 and Figure 3D). The incidence of HCC increased with each incremental "Rule-of-Five" category (Figure 4) from no cACLD (0.83 per 100 patient-years), to probable cACLD (1.49 per 100 patient-years) to certain cACLD-no CSPH (1.28–1.88 per 100 patient-years), and to probable CSPH (2.43 per 100 patient-years). HCC risk did not continue to increase substantially for those with certain CSPH with LS values beyond 25 kPa: 2.75 per 100 patient-years for LS 25–49.9 and 2.23 per 100 patient-years for LS 50–75. The HR per 5 kPa increase in LS above 25 kPa was nonsignificant (HR: 0.98, 95% CI: 0.93–1.03).

Associations between Baveno "Rule-of-Five" categories and composite outcome (death, decompensation, or HCC)

During the follow-up period, 2980 patients experienced the composite outcome (Table 2 and Figure 3E). The incidence of the composite outcome increased with each incremental

"Rule-of-Five" category (Figure 4) from no cACLD (4.86 per 100 patient-years), probable cACLD (5.97 per 100 patient-years), certain cACLD-no CSPH (6.11–7.15 per 100 patient-years), and to probable CSPH (9.22 per 100 patient-years). The rate of the composite outcome continued to increase for those with certain CSPH who had LS values beyond 25 kPa: those with LS 25–49.9 kPa experienced an event rate of 11.65 per 100 patient-years, which increased to 19.24 per 100 patient-years for those with LS 50–75 kPa ("critical CSPH").

Associations between Baveno "Rule-of-Five" categories and risk of adverse outcomes after adjustment for baseline characteristics

After adjusting for baseline age, sex, race/ethnicity, BMI, diabetes, Charlson comorbidity index, etiology of liver disease, and history of alcohol use, there were minimal differences between the crude and adjusted HR (Table 2). This suggests the absence of confounding by these factors in the associations between incremental Rule-of-Five category and adverse outcomes, that is, the associations are not explained by differences in the distribution of these factors.

Subgroup analyses for patients with MASLD and MASLD with BMI >30 kg/m^2

Among patients with MASLD (n = 3,739), risks of mortality (HR: 1.26, 95% CI: 1.14–1.38) and decompensation (HR: 1.75, 95% CI: 1.55–1.97) increased across higher "Rule-of-Five" categories (Supplemental Table S3, http://links.lww.com/HEP/J642). Compared to those with LS 25–49.9 kPa, those with LS 50–75 kPa ("critical CSPH") had a higher risk of mortality (8.49 vs. 5.17 per 100 patient-years) and decompensation (11.20 vs. 4.44 per 100 patient-years). Almost identical results were obtained among patients with MASLD who also had a BMI >30 kg/m^2 (n = 2875) (Supplemental Table S4, http://links.lww.com/HEP/J642). The incidence rates, HRs, and adjusted hazard ratios for decompensation or mortality by the "Rule-of-Five" category were very similar in the MASLD subgroup as in the entire population. HCC risk also increased with the incremental "Rule-of-Five" category (HR: 1.77, 95% CI: 1.36–2.31), but the absolute risks of HCC were lower in the MASLD subgroup than in all patients combined.

Sensitivity analyses accounting for active HCV, treatment for HCV, and for the competing risk of death

When excluding patients with active HCV from the analysis, we found similar associations between higher "Rule-of-Five" categories and mortality (HR: 1.40, 95% CI: 1.33–1.48), decompensation (HR: 1.97, 95% CI: 1.84–2.11), HCC (HR: 1.47, 95% CI: 1.31–1.64), and the composite outcome (HR: 1.54, 95% CI: 1.48–1.61) (Supplemental Table S5, http://links.lww.com/HEP/J642) as for the entire population. When censoring patients with active HCV at the time they achieved sustained virologic response during follow-up (if applicable), again similar associations were identified across higher "Rule-of-Five" categories (mortality HR: 1.36, CI: 95% 1.30–1.42, decompensation HR: 1.88, 95% CI: 1.77–1.66, HCC: 1.51, CI: 95% 1.40–1.62, and composite outcome HR: 1.48, 95% CI: 1.43–1.53) (Supplemental Table S6, http://links.lww.com/HEP/J642). Accounting for the competing risk of death using a competing risks analysis (Supplemental Table S7, http://links.lww.com/HEP/J642) resulted in subhazard ratios that were almost identical to the hazard ratios reported in Table 2.

DISCUSSION

In this retrospective cohort study of 17,076 US Veterans who underwent VCTE from May 2014 to January 2022, the risk of death and hepatic decompensation increased linearly across the Baveno "Rule-of-Five" categories, defined noninvasively by LS and platelet count, from no cACLD to probable cACLD, certain cACLD-no CSPH, probable CSPH, and certain CSPH. Furthermore, among patients with certain CSPH (LS ≥ 25 kPa), those with LS 50–75 kPa (which we labeled as "critical CSPH") had approximately double the risk of decompensation and mortality than those with LS 25–49.9 kPa, suggesting that the CSPH category could be further refined to improve risk stratification.

The "Rule-of-Five" has been well validated in diverse clinical populations, including those with chronic viral hepatitis, ALD, and non-obese MASLD.[7,8,13] However, it is expected that cACLD and CSPH will be dominated by MASLD in the near future. In patients with MASLD, an HVPG level ≥ 10 mm Hg, the gold-standard definition of CSPH, was associated with hepatic decompensation (10% after 2 y and 30.7% after 5 y, compared to 2.4% after 2 y and 9.4% after 5 y in patients without CSPH).[38] However, among patients with VCTE LS ≥ 25 kPa, the positive predictive value for CSPH as defined by HVPG ≥ 10 mm Hg was only 62.8% for patients with MASH and obesity, versus 91.7% for those with non-obese MASH and close to 100% for hepatitis B, C, and ALD.[13] Despite this, the Baveno "Rule-of-Five" categories achieved risk stratification for hepatic decompensation and death just as well in patients with MASLD in this current study, including the subset with obesity: absolute risks, HRs, and adjusted hazard ratios were very similar in these subgroups as in the entire population (Supplemental

Table S5, http://links.lww.com/HEP/J642). Taken together with other studies,[6–8,13] our results argue that the Baveno "Rule-of-Five" classification schema should be used in all patients with MASLD.

Current "Rule-of-Five" categories do not capture the excess risk of mortality and decompensation for patients with markedly elevated LS values beyond 25 kPa, all of whom are identified as having CSPH. We found that risks of mortality and decompensation were substantially higher in the 50–75 kPa group (9.85 and 11.24 per 100 patient-years, respectively) than in the 25–49.9 kPa group (6.98 and 4.20 per 100 patient-years, respectively). This argues that the CSPH category could be further subdivided into "certain CSPH" (LSM 25–49.9 kPa) and "critical CSPH" (LSM 50–75 kPa) to facilitate even better risk stratification. Physiologically, there is robust evidence to show that LS serves as a surrogate marker for the severity of portal hypertension, including for LS values above 25 kPa.[4] In one study of 326 patients with cirrhosis, HVPG levels were shown to correlate closely with LS: median LS values increased from 19.4 kPa for those with an HVPG >5 to <10 mm Hg, 25.8 kPa for those with HVPG 10–12 mm Hg, 37.1 kPa for those with HVPG >12 to ≤ 20 mm Hg, and 46.4 kPa for those with HVPG >20 mm Hg.[39]

The cACLD and CSPH categories shown in Figure 2 initially proposed by Pons et al[13] and adopted by the Baveno workshop, AASLD, and EASL provide a simple method of risk stratification that can be determined quickly in the clinic without requiring any computation. This "Rule-of-Five" categorizes the continuum of risk which is more precisely captured in predictive models for CSPH such as ANTICIPATE and ANTICIPATE-LRE.[6,37] Other risk scores have been proposed that potentially could achieve better risk stratification but also require additional computation. For example, the Agile 3+ and Agile 4 scores, which combine LS values with routinely available characteristics (AST/ALT ratio, platelet count, diabetes status, sex, and age) to generate a single score[40–42] were initially developed to predict the presence of significant fibrosis (Agile 3+) and advanced fibrosis (Agile 4), but subsequently have been shown to predict risk of liver decompensation and HCC, while additionally reductions in Agile scores over time indicated reduced risk of liver decompensation.[42] Another available tool is the fibrosis-5 score (www.fib5.net) which combines the components of the well-known FIB-4 score and LS to predict complications of portal hypertension.[43] In a large retrospective cohort of ~5800 US Veterans with chronic liver disease, the FIB-5 score demonstrated superior performance in predicting portal hypertension–associated complications as compared to LS or FIB-4 alone. However, additional studies in diverse settings are needed to further validate both the Agile 3+ and 4 and FIB-5 scores to assess their generalizability across different populations.

The "Rule-of-Five" categories did not track HCC risk as well as they tracked risk of hepatic decompensation or death. HCC risk did increase across higher "Rule-of-Five" categories but plateaued such that HCC incidence was highest for patients with LS 25–49.9 kPa (2.75 per 100 patient-years) and lower, but still substantial, for patients with LS 50–75 kPa (2.23 per 100 patient-years). This is not necessarily surprising given the "Rule-of-Five" categories were primarily established to assess the risk of portal hypertensive complications.

The strengths of our study include the application of the "Rule-of-Five" risk categories in a large cohort of patients undergoing clinically indicated VCTE in a large national health care system, with retrospective follow-up examining adverse outcomes identified through validated algorithms using their electronic health records. Therefore, our results reflect and likely apply to "real-world" practice where patients with known or suspected underlying liver disease are being evaluated with VCTE. Hepatic decompensation events and HCC were identified as documented in the comprehensive EHR. Although some events may have been missed, either because they were not clinically diagnosed or not documented, such outcome misclassification is unlikely to be significant and if present, would have attenuated the differences in risk between "Rule-of-Five" categories, that is, we would expect differences in risk between categories to be, if anything, even greater than what we describe. We also acknowledge several limitations. Our cohort was predominantly male as it reflects the US Veteran population. Median follow-up time was also limited to 2.8 years, and we were unable to assess for cause-specific mortality. In addition, while we were able to ascertain treatment status and outcome for patients with HCV, our ability to assess for modifying factors and treatment for other etiologies was unfortunately limited. We also did not assess for underlying right heart failure which leads to falsely elevated LS. As our study was conducted across the entire national VA health care system, there is likely heterogeneity in the implementation of VCTE, including operator expertise, pre-procedure instructions, and patient selection, which could impact results. This impact was mitigated, but not eliminated, by the inclusion of only results that met the $\leq 30\%$ IQR/M threshold. Finally, our results reflect the performance of the "rule-of-five" criteria in real-world clinical practice. We also acknowledge that VCTE, as a point-of-care testing that is typically available to subspecialty practices, may not be available to many patients seen at the VHA. As such, there is an element of selection bias that cannot be avoided.

In conclusion, the "Rule-of-Five" categories of cACLD and CSPH, as shown in the schema in Figure 2, were strongly and linearly associated with the risk of hepatic decompensation and death, which provides strong validation and justification for this novel, noninvasive, easy-to-use system of defining and

stratifying cACLD and CSPH. In addition, our findings expand upon this risk classification system: risks of death and decompensation continued to rise beyond LS >25 kPa, such that patients with LS 50–74.9 kPa had substantially higher risks of decompensation and death (but not HCC) than those with LS 25–49.9 kPa. This indicates an easy-to-execute opportunity to improve the schema by subcategorizing LS values >25 kPa into LS 25–49.9 kPa (certain CSPH) and LS 50–74.9 kPa (critical CSPH).

DATA AVAILABILITY STATEMENT

Analytic methodology and data may be made available to other researchers if requested.

AUTHOR CONTRIBUTIONS

Guarantor of the article: Philip Vutien. Study conceptualization/design: Philip Vutien, Abbey Barnard Giustini, and George N. Ioannou. Data curation: Joleen A. Borgerding, Philip Vutien, Kristin Berry, and George N. Ioannou. Formal analysis: Philip Vutien. Investigation: Philip Vutien, Abbey Barnard Giustini, Nicole J. Kim, Joleen A. Borgerding, Kay M. Johnson, Trang VoPham, Andrew M. Moon, Chun-Nan Hsu, Kristin Berry, Lauren A. Beste, and George N. Ioannou. Methodology: Philip Vutien, Abbey Barnard Giustini, and George N. Ioannou. Supervision: George N. Ioannou. Writing—original draft: Philip Vutien, Abbey Barnard Giustini, and George N. Ioannou. Writing—review and editing: Philip Vutien, Abbey Barnard Giustini, Nicole J. Kim, Andrew M. Moon, Chun-Nan Hsu, Joleen A. Borgerding, Kay M. Johnson, Trang VoPham, Kristin Berry, Lauren A. Beste, Catherine Mezzacappa, David E. Kaplan, Tamar H. Taddei, and George N. Ioannou.

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CONFLICTS OF INTEREST

Nicole J. Kim received grants from Madrigal. Andrew M. Moon consults for TARGET RWE and Intercept. He received grants from DCN Diagnostics. David E. Kaplan advises and received grants from AstraZeneca. He advises Sirtex and Exelixis. He received grants from Roche Genentech, Exact Sciences, and Glycotest. Tamar H. Taddei is the treasurer of and governing board member of AASLD. The remaining authors have no conflicts to report.

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