Prognosis of French COVID-19 patients with chronic liver disease:

A national retrospective cohort study for 2020

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the Demosthenes research group

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Methods: ICD-10 and French common classification of medical procedures

Acute_kidney_injury, N17, JVJF002, JVJF003, JVJF005, JVJF006, JVJF007, JVJF005, JVJB002,

Acute_liver_failure, K720, K729,

Acute_respiratory_failure, J960, J962, J969, J80,

Aids, B20, B21, B22, B24,

Alcoholic_liver_disease, K70,

Arterial_embolism_and_thrombosis, I74,

Ascitis, R18, HPHB003, HPJB001,

Alcohol_use_disorders, E244, E511, F101, F102, F103, F104, F105, F106, F107, F108, F109, F1020, F1021, F1022, F1023, G312, G621, G721, I426, K292, K70, K852, K860, O354, Z502, Z714, Z721,

Autoimmune_hepatitis, K754,

Budd_chiari_syndrome, I820,

Intrahepatic_cholangiocarcinoma, C221,

Cerebral_infarction, I63,

Cerebrovascular_disease, G45, G46, H340, I6,

Cholangitis, K830, K831, K835, K835, K8705, R17,

Chronic_kidney_disease_advanced, I120, I131, N00, N01, N03, N05, N183, N184, N185, N19, N250, Z490, Z491, Z492, Z940, Z992, HGPC005, HPGA001, HPJP001, HPKA002, HPKB001, HPKC014, HPLA005, HPLB004, HPLC035, HPPA004, HPPP002, JVRP007, JVRP008, JAEA003, JVJB001,JVRP004, JVJF004, JVJF008, JVQF001, JVQF007, JVQP002, JVQP009, YYYY007,

Chronic_kidney_disease, E102, E112, E122, E132, E142, I151, JAHB001, JAHH002, JAHC001, JAHA001, JAHJ006, JAHJ007, N02, N04, N06, N07, N08, N181, N182, N19, N25, N083,

Chronic_obstructive_pulmonary_disase, I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703,

Cirrhosis, I859, I864, I982, I9829, K703, K717, K743, K744, K745, K746, K766,

Congestive_heart_failure, I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I43, I50, P290,

Connective_tissue_disorder, M05, M06, M315, M32, M33, M34, M351, M353, M360,

Covid_19, U0710, U0711, U0712, U0714, U0715,

Covid_19_sequellae, U089, U099, U109,

Covid_19_sirs, U109,

Decompensated_cirrhosis, **Cirrhosis** & (R17, K704, K711, K72, K767, I280, I850, I983, I9820, R18, J948, K65, EHBD001, EHNE002, HESE001, HESE002, HPHB003, HPJB001, EHCA003, EHCA006, EHCA009, EHCA007, EHCA004, EHCA002, EHCA005, EHCA010, EHCA001, HEPA005, HEPA004, HEPA007),

Dementia, F00, F01, F02, F03, F051, G30, G311,

Diabetes_mellitus_complicated, E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E113, E114, E115, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147, H360, N083, H280, G632,

Diabetes_mellitus_uncomplicated, E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149,

Diabetes_mellitus, E1,

Eccor, GLJF010,

Embolism_and_thrombosis_of_renal_vein, I828,

Embolism_and_thrombosis_of_unspecified_vein, I829,

Embolism_and_thrombosis_of_vena_cava, I822,

Flu, J09, J10, J11,

Gastro_esophageal_varices_bleeding, I850, I983, I9820, EHBD001, EHNE002, HESE001, HESE002,

Gastro_esophageal_varices_not_bleeding, I859, I864, I982, I9829,

Hemiplegia, G041, G114, G801, G802, G81, G82, G830, G831, G832, G833, G834, G839,

Hepatitis_B_virus, B181, B162, B169,

Hepatitis_C_virus, B182,

Hepatitis_D_virus, B160, B161, B180, B170,

Hepatic_encephalopathy, K704, K711, K74,

Hepatocellular_carcinoma, C220,

Hepatopulmonary_syndrome, I280,

Hepatorenal_syndrome, K767,

Hydrothorax, J948,

Hypercholesterolemia_pure, E870,

Hyperlipemia_mixed, E782,

Hyperlipemia, E780, E781, E782, E784, E785,

Hypertension, I10, I11, I12, I13, R030,

Hypertensive_heart_failure_with_or_without_renal_failure, I10, I130, I132,

Hypertriglyceridemia, E871,

Jaundice, R17,

Leukemia, C91, C92, C93, C94, C95, C96,

Liver_biopsy, HLHB001, HLHJ003, HLHJ006, HLHH006, HLHJ005, HLHH007, HLHH001, HLHH005,

Liver_disease_mild, K713, K714, K715, K73, K740, K741, K742, K743, K760, K764, K765,

Liver_disease_moderate_to_severe, K703, I850, I859, I864, I982, J948, K703, K704, K711, K717, K721, K729, K744, K745, K746, K65, K66, K767, R17, R18, EHBD001, EHNE002, HESE001, HESE002, HPHB003, HPJB001, EHCA003, EHCA006, EHCA009, EHCA007, EHCA004, EHCA002, EHCA005, EHCA010, EHCA001, HEPA005, HEPA004, HEPA007,

Liver_transplantation, Z944, HLEA001, HGEA002, HLEA002, HGEA004,

Lymphoma, C81, C82, C83, C84, C85, C86, C87, C89, C90,

Mechanical_ventilation, GLLD004, GLLD005, GLLD006, GLLD007, GLLD008, GLLD009, GLLD012, GLLD013, GLLD015, DKMD001, GEPA004, GELD002, GELD004,

Myocardial_infarction, I21, I22, I252,

Obesity, E66,

Other_cause_of_chronic_liver_disease, E831, E84, FEJF003, FEJF006, FEJF008, E830, N163, I820, K743, K754, K830, Q44, T864, Z944,

Other_diabetes_mellitus, E12, E13, E14,

Other_primary_liver_cancers, C222, C223, C224, C227, C229,

Oxygen_therapy, GLLD002, GLLD003, GLLD017, GLLD019,

Paraplegia_hemiplegia, G041, G114, G801, G802, G81, G82, G830, G831, G832, G833, G834, G839,

Peptic_ulcer_disease, K25, K26, K27, K28,

Peripheral_vascular_disease, I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, R02, Z958, Z959,

Phlebitis_and_thrombophlebitis, I80,

Plasma_exchange, FEJF001, FEJF002,

Portal_hypertension, K766,

Portal_vein_thrombosis, I81,

Primary_liver_cancer, C220, C221, C229,

Pulmonary_embolism, I26,

Renal_transplantation, T861, Z940, JAEA003,

Renal_replacement_therapy, JVJF002, JVJF003, JVJF005, JVJF006, JVJF007, JVJF005, JVJB002,

Smoking, F17, Z716, Z720, T652,

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Solid_tumor_metastatic, C77, C78, C79, C80,

Splanchnic_thrombophlebitis, I81, I82,

Surgical_shunt, EHCA003, EHCA006, EHCA009, EHCA007, EHCA004, EHCA002, EHCA005, EHCA010, EHCA001, HEPA005, HEPA004, HEPA007,

Thrombophlebitis_migrans, I821,

TIPS, EHCF002, EHAF004, EHPF001, EHNF001,

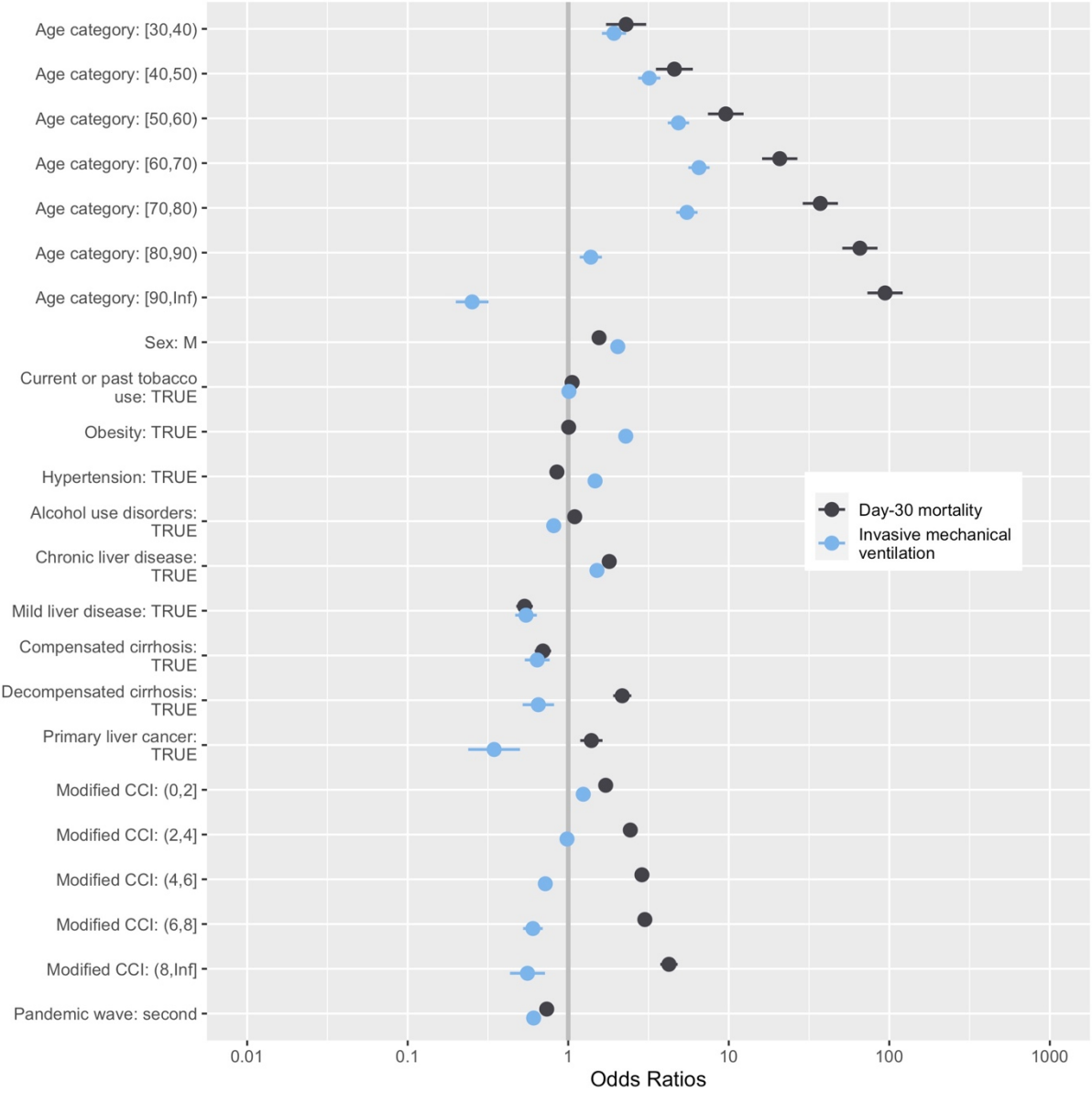**Transfusion**, FELF003, FELF004,

Transplant_recipient_without_liver, Z940, Z941, Z942, Z943, Z9481, Z9482, T861, T862, T863, T8680, T8681, T8682, Z94801, Z94802, Z94803, Z94804, Z94809, T860, JAEA003,

Type_1_diabetes_mellitus, E10,

Type_2_diabetes_mellitus, E11,

Vasopressors, EQLF001, EQLF001

Fig. S1: Interaction between alcohol use disorders and first and second pandemic waves

Odds ratios were computed with multivariate binary logistic regressions. Data are for patients who were hospitalized for Covid-19 between February 1 and December 31, 2020 in Metropolitan France. The 2011-2020 French National Patient Registry was used to identify underlying conditions before Covid-19. The Charlson comorbodity index predicts 10-year survival in patients with multiple comorbidities, and ranges from 0 to 39, with higher scores indicating higher frailty. Decompensated cirrhosis was cirrhosis with ascitis, hypertensive bleeding, non-obstructive jaundice, or encephalopathy, before Covid-19. Note: M: Male; F: Female"

Table S1: Charlson comorbidity index by chronic liver disease

Characteristic	Overall, N = 259,110[1]	Chronic liver disease		p-value[2]
		No, n = 243,634[1]	Yes, n = 15,476[1]	
Acquired immunodeficiency syndrome	1,118 (0.4%)	893 (0.4%)	225 (1.5%)	<0.001
Cerebrovascular accident with minor or no residua and transient ischemic attacks	12,403 (4.8%)	11,231 (4.6%)	1,172 (7.6%)	<0.001
Chronic kidney disease	31,820 (12%)	28,317 (12%)	3,503 (23%)	<0.001
Chronic obstructive pulmonary disease	33,781 (13%)	30,938 (13%)	2,843 (18%)	<0.001
Congestive heart failure	47,420 (18%)	43,026 (18%)	4,394 (28%)	<0.001
Connective tissue disease	4,328 (1.7%)	3,975 (1.6%)	353 (2.3%)	<0.001
Dementia	28,419 (11%)	27,144 (11%)	1,275 (8.2%)	<0.001
Diabetes mellitus	56,982 (22%)	51,555 (21%)	5,427 (35%)	<0.001
Hemiplegia	12,518 (4.8%)	11,410 (4.7%)	1,108 (7.2%)	<0.001
Leukemia	2,607 (1.0%)	2,316 (1.0%)	291 (1.9%)	<0.001
Myocardial infarction	5,539 (2.1%)	4,941 (2.0%)	598 (3.9%)	<0.001
Lymphoma	3,500 (1.4%)	3,123 (1.3%)	377 (2.4%)	<0.001
Peptic ulcer disease	1,696 (0.7%)	1,063 (0.4%)	633 (4.1%)	<0.001
Peripheral vascular disease	19,200 (7.4%)	16,914 (6.9%)	2,286 (15%)	<0.001
Solid tumor	23,160 (8.9%)	19,610 (8.0%)	3,550 (23%)	<0.001
At least one severe comorbidity	145,363 (56%)	133,208 (55%)	12,155 (79%)	<0.001

Data are for patients who were discharged after Covid-19 between February 1 and December 31, 2020 in France. The 2011-2020 French National Patient Registry was used to identify underlying conditions before Covid-19.

[1] n (%)

[2] Pearson's Chi-squared test

Table S2: Multivariate risks for mechanical ventilation after Covid-19

Predictors	Odds Ratios	CI	p
	Mechanical ventilation		
(Intercept)	0.01	0.01 – 0.01	**<0.001**
Age category: [30,40)	1.94	1.63 – 2.31	**<0.001**
Age category: [40,50)	3.27	2.78 – 3.83	**<0.001**
Age category: [50,60)	5.05	4.33 – 5.89	**<0.001**
Age category: [60,70)	6.93	5.95 – 8.07	**<0.001**
Age category: [70,80)	5.91	5.07 – 6.89	**<0.001**
Age category: [80,90)	1.51	1.29 – 1.77	**<0.001**
Age category: [90,Inf)	0.28	0.22 – 0.35	**<0.001**
Sex: M	2.04	1.97 – 2.11	**<0.001**
Current or past tobacco use: TRUE	1.03	0.97 – 1.10	0.265
Obesity: TRUE	2.32	2.23 – 2.40	**<0.001**
Hypertension: TRUE	1.52	1.47 – 1.58	**<0.001**
Alcohol use disorders: TRUE	0.82	0.76 – 0.89	**<0.001**
Chronic liver disease: TRUE	1.54	1.44 – 1.64	**<0.001**
Mild liver disease: TRUE	0.55	0.47 – 0.64	**<0.001**
Compensated cirrhosis: TRUE	0.64	0.53 – 0.76	**<0.001**
Decompensated cirrhosis: TRUE	0.65	0.52 – 0.81	**<0.001**
Primary liver cancer: TRUE	0.34	0.24 – 0.50	**<0.001**
Modified CCI: [2,4)	0.97	0.93 – 1.01	0.121
Modified CCI: [4,6)	0.73	0.68 – 0.77	**<0.001**
Modified CCI: [6,8)	0.54	0.48 – 0.59	**<0.001**
Modified CCI: [8,Inf]	0.56	0.48 – 0.66	**<0.001**
Pandemic wave: second	0.61	0.59 – 0.63	**<0.001**
Observations	259,109		
R² Tjur	0.067		

Data are for patients who were discharged after Covid-19 between February 1 and December 31, 2020 in France. The 2011-2020 French National Patient Registry was used to identify underlying conditions before Covid-19. Mild liver disease was chronic liver disease without cirrhosis. Decompensated cirrhosis was cirrhosis with ascites, hypertensive bleeding, non-obstructive jaundice, or encephalopathy, before Covid-19. The Charlson comorbidity index predicts 10-year survival in patients with multiple comorbidities, and ranges from 0 to 30, without entering age and liver disease, with higher scores indicating higher frailty. Note: CCI : Charlson comorbidity index; M: Male

Table S3: Multivariate risks for day-30 mortality after Covid-19

	Day-30 mortality		
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.00	0.00 – 0.01	**<0.001**
Age category: [30,40)	2.33	1.74 – 3.11	**<0.001**
Age category: [40,50)	4.77	3.66 – 6.22	**<0.001**
Age category: [50,60)	10.19	7.89 – 13.17	**<0.001**
Age category: [60,70)	22.72	17.63 – 29.29	**<0.001**
Age category: [70,80)	41.24	32.01 – 53.13	**<0.001**
Age category: [80,90)	74.07	57.51 – 95.40	**<0.001**
Age category: [90,Inf)	107.49	83.41 – 138.52	**<0.001**
Sex: M	1.56	1.52 – 1.59	**<0.001**
Current or past tobacco use: TRUE	1.08	1.03 – 1.13	**0.002**
Obesity: TRUE	1.02	0.99 – 1.05	0.155
Hypertension: TRUE	0.87	0.85 – 0.89	**<0.001**
Alcohol use disorders: TRUE	1.11	1.05 – 1.17	**<0.001**
Chronic liver disease: TRUE	1.79	1.71 – 1.87	**<0.001**
Mild liver disease: TRUE	0.54	0.48 – 0.61	**<0.001**
Compensated cirrhosis: TRUE	0.71	0.63 – 0.80	**<0.001**
Decompensated cirrhosis: TRUE	2.21	1.94 – 2.51	**<0.001**
Primary liver cancer: TRUE	1.38	1.17 – 1.62	**<0.001**
Modified CCI: [2,4)	1.82	1.77 – 1.86	**<0.001**
Modified CCI: [4,6)	2.14	2.07 – 2.22	**<0.001**
Modified CCI: [6,8)	2.40	2.27 – 2.52	**<0.001**
Modified CCI: [8,Inf]	3.11	2.86 – 3.39	**<0.001**
Pandemic wave: second	0.73	0.72 – 0.75	**<0.001**
Observations	259,109		
R^2 Tjur	0.137		

Data are for patients who were discharged after Covid-19 between February 1 and December 31, 2020 in France. The 2011-2020 French National Patient Registry was used to identify underlying conditions before Covid-19. Mild liver disease was chronic liver disease without cirrhosis. Decompensated cirrhosis was cirrhosis with ascites, hypertensive bleeding, non-obstructive jaundice, or encephalopathy, before Covid-19. The Charlson comorbidity index predicts 10-year survival in patients with multiple comorbidities, and ranges from 0 to 30, without entering age and liver disease, with higher scores indicating higher frailty. Note: CCI : Charlson comorbidity index; M: Male

Table S4: Characteristics of propensity-matched Covid-19 patients by primary liver cancer

Characteristic	Overall, N = 1,182[1]	Primary liver cancer		p-value[2]
		No, n = 591[1]	Yes, N = 591[1]	
Mechanical ventilation	186 (16%)	112 (19%)	74 (13%)	0.002
Age category				>0.9
[18,30)	13 (1.1%)	6 (1.0%)	7 (1.2%)	
[30,40)	10 (0.8%)	5 (0.8%)	5 (0.8%)	
[40,50)	55 (4.7%)	28 (4.7%)	27 (4.6%)	
[50,60)	116 (9.8%)	57 (9.6%)	59 (10.0%)	
[60,70)	327 (28%)	165 (28%)	162 (27%)	
[70,80)	424 (36%)	212 (36%)	212 (36%)	
[80,90)	206 (17%)	103 (17%)	103 (17%)	
[90,Inf]	31 (2.6%)	15 (2.5%)	16 (2.7%)	
Sex				0.9
F	354 (30%)	176 (30%)	178 (30%)	
M	828 (70%)	415 (70%)	413 (70%)	
Obesity	276 (23%)	137 (23%)	139 (24%)	0.9
Hypertension	719 (61%)	362 (61%)	357 (60%)	0.8
Diabetes mellitus	497 (42%)	250 (42%)	247 (42%)	0.9
Day-30 mortality	341 (29%)	168 (28%)	173 (29%)	0.7
Modified CCI	3 (1, 6)	3 (1, 6)	3 (1, 6)	>0.9

Data are for patients who were discharged after Covid-19 between February 1 and December 31, 2020 in France. The 2011-2020 French National Patient Registry was used to identify underlying conditions before Covid-19. Mild liver disease was chronic liver disease without cirrhosis. Advanced cirrhosis was cirrhosis with ascites, hypertensive bleeding, non-obstructive jaundice, or encephalopathy, before Covid-19. The Charlson comorbidity index predicts 10-year survival in patients with multiple comorbidities, and ranges from 0 to 30, without entering age and liver disease, with higher scores indicating higher frailty. Note: CCI: Charlson comorbidity index. M: Male; F: Female

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Wilcoxon rank sum test