

Supplementary Data

Supplementary Table 1: ICD coding used to extract data

	ICD 10 coding
Etiology	<p>Hepatitis B: B18.0, B18.1</p> <p>Hepatitis C: B18.2</p> <p>Other Viral Hep: B18.8, B18.9, B19</p> <p>Alcohol: K70.2, K70.3</p> <p>NASH: K75.8, K76.0</p> <p>AIH: K75.4</p> <p>PBC: K74.3, K74.4, K74.5</p> <p>Cardiac: K71.7, K76.1</p>
Hepatic Decompensation (defined by EASL guidelines)	<p>Liver Failure: K72.0, K72.1, K72.9</p> <p>Hepatorenal syndrome: K76.7</p> <p>Hepatic Encephalopathy: K72.90</p> <p>Spontaneous bacterial peritonitis: K65.2, K65.0, K65.9</p> <p>Ascites: R18</p> <p>Liver cell carcinoma C22.0</p> <p>Variceal Bleeding: I85.0, I98.3, I98.2, I85.9</p>
Medical Comorbidities	<p>DM with complications: E10-14.0-1,6-8</p> <p>DM with end organ damage: E10-14.2-5</p> <p>Malignant Neoplasms: C00-C97</p> <p>Solid organ primary: C00-75</p> <p>Metastatic cancer: C76-80, C97</p> <p>Hematological malignancy: C81-96</p> <p>HIV/AIDS: B20-24</p> <p>Chronic Kidney Disease: N18-N19</p> <p>Moderate to severe CKD: N18.3-5, N19</p> <p>Ischemic Heart Disease: I20-I25</p>

Heart Failure: I25.5, I50

MI: I20.0-1, I21-25

Peripheral Vascular Disease: I73

Cerebrovascular Diseases: I60-I69

TIA: G45

Hemiplegia: G81-82

Chronic Obstructive Lung Disease: J40-47

Dementia: F0-F3

Connective Tissue Disorder: M30-M36

Peptic Ulcer Disease: K25- K27

Supplementary Table 2: List of Medications Analysed (available in Singapore)

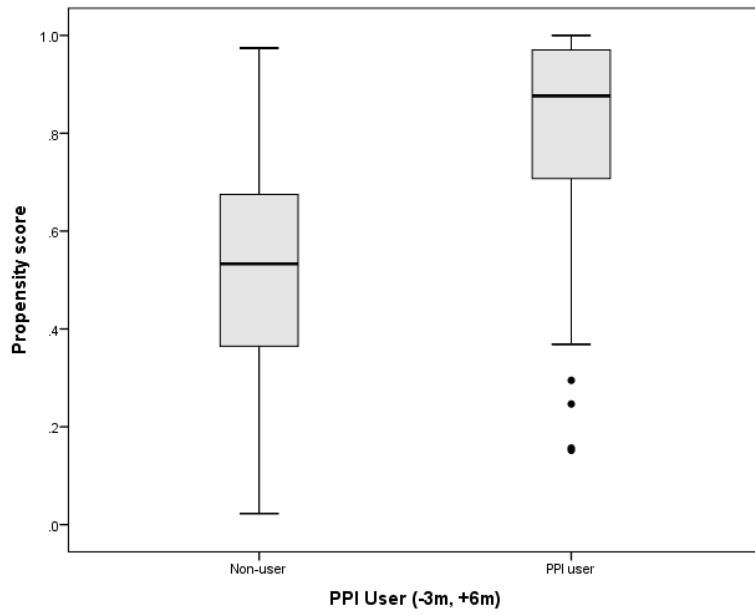
Type of Medication	Name of Medication
Proton Pump Inhibitors	Omeprazole Dexlansoprazole Esomeprazole Pantoprazole Rabeprazole
Type 2 Diabetes Medications	Insulin Novorapid Actrapid Apidra Lispro Glulisine Insulatard Mixtard Novomix Levemir Detemir Lantus Glargine Sulphonylurea Glipizide Tolbutamide Glimepiride Glyburide Glibenclamide Gliclazide

	<p>Thiazolidinedione</p> <p>Pioglitazone</p> <p>Biguanide</p> <p>Metformin</p> <p>DPP-4 Inhibitor</p> <p>Linagliptin</p> <p>Vildagliptin</p> <p>Sitagliptin</p> <p>Other</p> <p>Acarbose</p>
Statins	<p>Atorvastatin</p> <p>Lovastatin</p> <p>Pravastatin</p> <p>Rosuvastatin</p> <p>Simvastatin</p>
Beta Blockers ¹	<p>Nonselective beta blocker</p> <p>Propranolol</p> <p>Carvedilol</p> <p>Cardioselective beta blocker</p> <p>Labetelol</p> <p>Sotalol</p> <p>Timolol</p> <p>Acebutolol</p>

	<p>Atenolol</p> <p>Betaxolol</p> <p>Bisoprolol</p> <p>Metoprolol</p> <p>Nebivolol</p> <p><i>¹Nadolol was not available in Government Restructured Hospitals in Singapore</i></p>
Anti-Platelets	<p>Aspirin</p> <p>Other anti-platelet agents</p> <p>Prasugrel</p> <p>Clopidogrel</p> <p>Ticagrelor</p> <p>Ticlopidine</p> <p>Eptifibatide</p> <p>Dipyridamole</p>
ACE-I/ ARB	<p>Enalapril</p> <p>Ramipril</p> <p>Perindopril</p> <p>Lisinopril</p> <p>Valsartan</p> <p>Telmisartan</p> <p>Losartan</p> <p>Irbesartan</p> <p>Candesartan</p>
Antiviral	<p>Nucleoside Analogues</p> <p>Lamivudine</p> <p>Adefovir</p> <p>Entecavir</p> <p>Tenofovir</p>

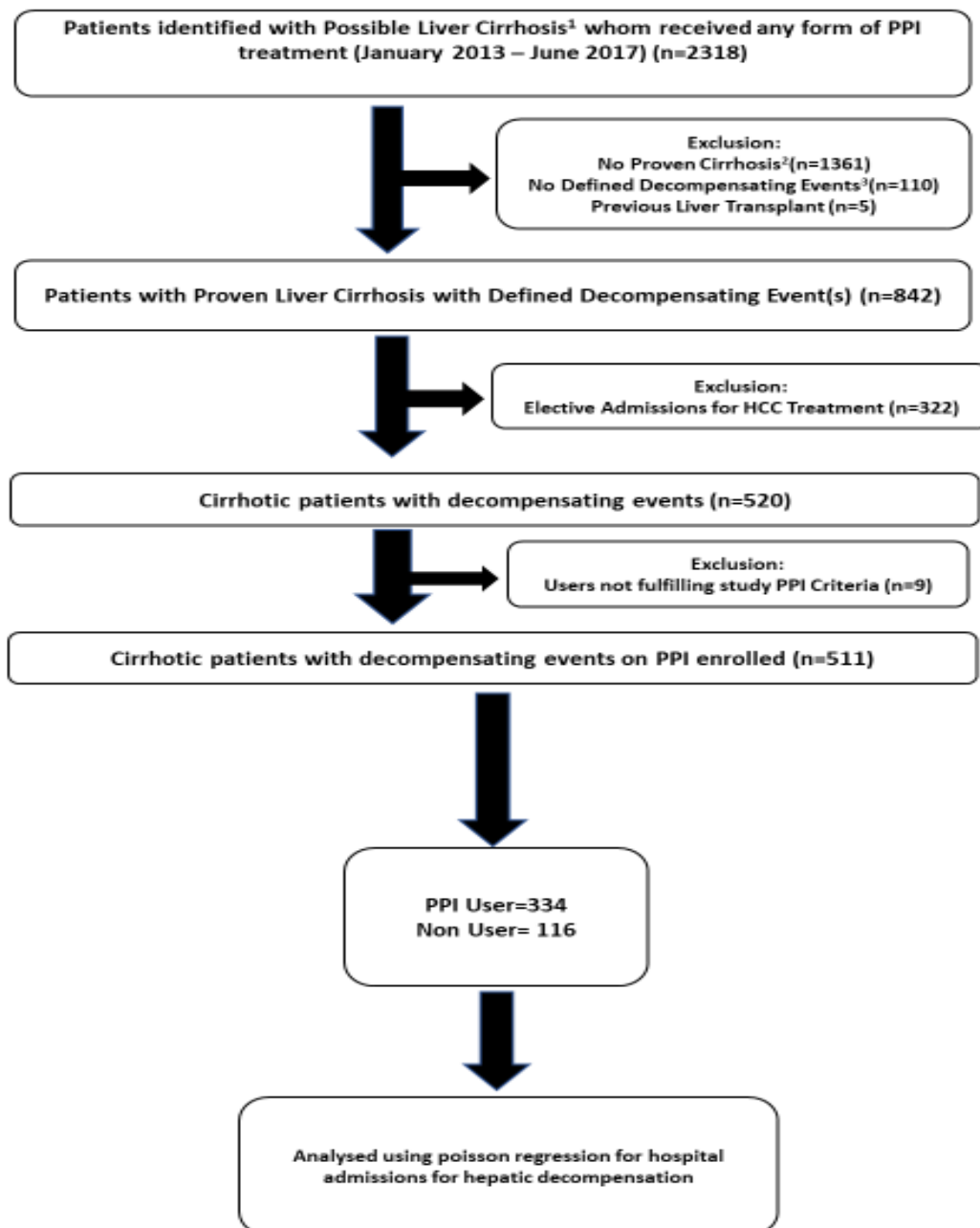
	<p>Direct Acting Antivirals (DAA)²</p> <p>Sofosbuvir</p> <p>Daclatasvir</p> <p>Ribavirin</p> <p>Ledipasvir</p> <p><i>²Available DAAs in Singapore during study period</i></p>
<p>Antibiotics (SBP prophylaxis) ³</p>	<p>Ciprofloxacin</p> <p><i>³Norfloxacin was not available in Government Restructured Hospitals in Singapore.</i></p> <p><i>Rifaximin was not available in Singapore at the time of study.</i></p> <p><i>There were a total of 19 patients on long term fluoroquinolone (results were not included in the main table).</i></p>

Supplementary Figure 1: Propensity score Boxplot for 6 month landmark period



Mann Whitney U test, $p < 0.001$

Supplementary Figure 2: Consort Diagram for Hospital Admissions for Hepatic Decompensation in Patients with Decompensated Liver Cirrhosis



- 1 Cohort selected based on complications that are possibly caused by Liver Cirrhosis (e.g. Encephalopathy, Ascites, Variceal Bleeding). The underlying cause was originally not defined – based on ICD 9 and ICD 10
- 2 Cirrhosis proven by Imaging modalities (CT, MRI, Fibroscan, Ultrasound) or liver biopsy
- 3 Defined Decompensating Events: Ascites, SBP, Hepatic Encephalopathy, Bleeding Varices, HRS, Liver Failure
- 4 PPI Users defined as patients receiving a cumulative defined daily dose >28

Supplementary Table 3: Subgroup Analyses of Mortality of Proton Pump Inhibitor Users and Non-users with Decompensated Liver Cirrhosis

6-month Landmark Period	N	Adjusted HR (95% CI)	<i>p-value</i>
Viral Hepatitis Aetiology	Non-User = 21 PPI User = 94	3.23(0.99 - 10.52)	0.052
NASH / Cryptogenic Aetiology	Non-User = 16 PPI User = 98	2.16 (0.78 - 5.99)	0.140
Ascites on Index Admission	Non-User = 37 PPI User= 121	1.91 (0.96 - 3.78)	0.063
History of previous hepatic decompensation	Non-User= 15 PPI User= 68	1.96 (0.77 - 4.99)	0.114
No prior history of decompensation	Non-User = 42 PPI User= 170	1.99 (0.98 - 4.00)	0.054
Without SBP or HE at baseline	Non-User = 44 PPI User= 164	1.90 (0.98 – 3.71)	0.059
With SBP or HE at baseline	Non-User = 13 PPI User= 74	2.21 (0.78-6.21)	0.134
Type 2 Diabetes	Non-User = 24 PPI User= 133	1.11 (0.55 - 2.25)	0.769
No previous history of malignancy or HCC	Non-User= 47 PPI User= 199	2.04 (1.09 - 3.83)	0.030

Previous History of Malignancy or HCC	Non-User = 10 PPI User = 39	2.21 (0.65 - 7.46)	0.203
MELD \geq 15	Non-User = 14 PPI User = 59	10.30 (1.41 - 75.58)	0.022
MELD < 15	Non-User = 43 PPI User = 179	1.44 (0.79 - 2.61)	0.234

PPI: Proton Pump Inhibitor

HR: Hazard Ratio

MELD: Model for End Stage Liver Disease

NASH: Non-alcoholic Steatohepatitis

HCC: Hepatocellular Carcinoma

CI: Confidence Interval

Supplementary Table 4: Baseline Characteristics of Proton Pump Inhibitor Users and Non-Users for Hospital Admissions for Hepatic Decompensation

Baseline characteristics	Non-User (n = 116)	PPI user (n = 334)	p-value
Gender			
Male	78 (67.2%)	232	0.66
Female		(69.5%)	
Age (years)	63.1 ± 13.4	64.9 ± 13.0	0.21
Race			0.82
Chinese	75 (64.7%)	200	
Malay	19 (16.4%)	(59.9%)	
Indian	13 (11.2%)	66 (19.8%)	
Others	9 (7.8%)	41 (12.3%)	
		27 (8.1%)	
Etiology of Cirrhosis			0.02
Hepatitis B	32 (27.6%)	58 (17.4%)	
Alcohol	22 (19.0%)	53 (15.9%)	
Hepatitis C	16 (13.8%)	67 (20.1%)	
NASH	24 (20.7%)	107	
Autoimmune	6 (5.2%)	(32.0%)	
Others	16 (13.8%)	8 (2.4%)	
		41 (12.3%)	
Index Hepatic Event:			
HCC	27(23.3%)	44(13.2%)	0.01
Ascites	78 (67.2%)	187	0.03
SBP	12(10.3%)	(56.0%)	0.33
HE	27(23.3%)	25(7.5%)	0.88
Variceal Bleed	15(12.9%)	80(24.0%)	0.04
		72(21.6%)	
Previous Hepatic Event:			
HCC	5 (4.3%)	13 (3.9%)	0.79
Ascites	14 (12.1%)	42 (12.6%)	0.89
HE	2 (1.7%)	14 (4.2%)	0.38
Variceal Bleed	11 (9.5%)	54 (16.2%)	0.08
SBP	2 (1.7%)	8 (2.4%)	1.00

Biochemical Results at Baseline:			
Mean (\pm SD)			
Albumin (g/L)	26.1(5.2)	27.1 (6.3)	0.09
INR	1.4(0.8)	1.2(0.3)	0.02
Creatinine (umol/L)	149.7(134.6)	136.2(153.7)	0.40
Bilirubin (umol/L)	75.2(88.7)	45.9(58.3)	0.001
Platelet Count ($10^9/L$)	132.0(101.6)	134.8(88.3)	0.78
Haemoglobin (g/dL)	10.9(2.7)	10.7(2.6)	0.47
MELD			
Median (IQR)	14.0 (10.0-21.0)	12.0 (8.8-17.0)	< 0.001
Medical Comorbidities			
GERD	0 (0.0%)	23 (6.9%)	0.004
Esophagitis	4 (3.4%)	22 (6.6%)	0.21
Peptic Ulcer Disease	5 (4.3%)	41 (12.3%)	0.02
DM¹			
None	60 (51.7%)	148	0.18
Uncomplicated	22 (19.0%)	(44.3%)	
End-organ damage	34 (29.3%)	91 (27.2%) 95 (28.4%)	
Malignancy¹			
None	83 (71.6%)	264	0.24
Leukemia/Lymphoma/Localised solid tumor	23 (19.8%)	(79.0%) 51 (15.3%)	
Metastatic solid tumor	10 (8.6%)	19 (5.7%)	
HIV/AIDS ¹	3 (2.6%)	2 (0.6%)	0.11
Renal Impairment ¹	27 (23.3%)	84 (25.1%)	0.69
Congestive Heart Failure ¹	7 (6.0%)	40 (12.0%)	0.07
Myocardial Infarct ¹	12 (10.3%)	48 (14.4%)	0.27
COPD ¹	4 (3.4%)	14 (4.2%)	1.00
PVD ¹	0 (0.0%)	5 (1.5%)	0.33
CVA/TIA ¹	5 (4.3%)	34 (10.2%)	0.05

Dementia ¹	5 (4.3%)	15 (4.5%)	0.94
Hemiplegia ¹	0 (0.0%)	5 (1.5%)	0.33
Connective Tissue Disease ¹	3 (2.6%)	4 (1.2%)	0.38
Baseline Medications:			
Chronic HBV on antivirals	14/32	19/58	0.30
Chronic HCV treated with DAA ²	0/16	3/64	1.0
Use of other concurrent medications (>3 months use)			
Insulin	4 (3.4%)	54 (16.2%)	< 0.001
Sulphonylureas	10 (8.6%)	64 (19.2%)	0.01
Insulin sensitizers	4 (3.4%)	26 (7.8%)	0.11
Metformin	8 (6.9%)	58 (17.4%)	0.01
DPP4 Inhibitors	6 (5.2%)	4 (1.2%)	0.02
Antiplatelet	6 (5.2%)	66 (19.8%)	< 0.001
Aspirin	6 (5.2%)	55 (16.5%)	0.002
Statins	3 (2.6%)	41 (12.3%)	0.002
ACE-I/ARB	6 (5.2%)	57 (17.1%)	0.001
Nonselective Beta Blockers	10 (8.6%)	101 (30.2%)	< 0.001
Selective Beta Blockers	4 (3.4%)	39 (11.7%)	0.01

NASH- Non Alcoholic Steatohepatitis

MELD – Model of End-stage Liver Disease;

GERD- Gastroesophageal Reflux Disease

DM – Diabetes Mellitus

HIV/AIDS- Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

COPD-Chronic Obstructive Pulmonary Disease

PVD-Peripheral Vascular Disease

CVA/TIA- Cerebrovascular Accident/Transient Ischemic Attack

DPP4-Dipeptidyl Peptidase-4

ACE-I/ARB-Angiotensin Converting Enzyme Inhibitor/Angiotensin II Receptor Blocker

DAA – Direct Acting Antiviral

¹ As defined by Charlson comorbidity index

² 3 patients were given 12 weeks of sofosbuvir/daclatasvir/ribavirin for HCV cirrhosis; DAA therapy only became fully funded in early 2017