Supplementary Data

Supplementary Table 1: ICD coding used to extract data

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

	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)

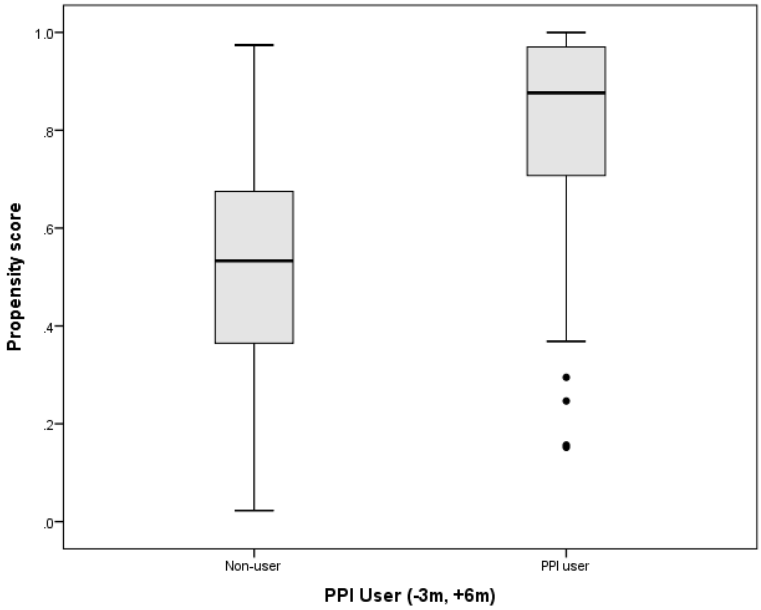
Type of Medication	**Name of Medication**
Proton Pump Inhibitors	Omeprazole Dexlansoprazole Esomeprazole Pantoprazole Rabeprazole
Type 2 Diabetes Medications	**Insulin** Novorapid Actrapid Apidra Lispro Glulisine Insulatard Mixtard Novomix Levemir Detemir Lantus Glargine **Sulphonylurea** Glipizide Tolbutamide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

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

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

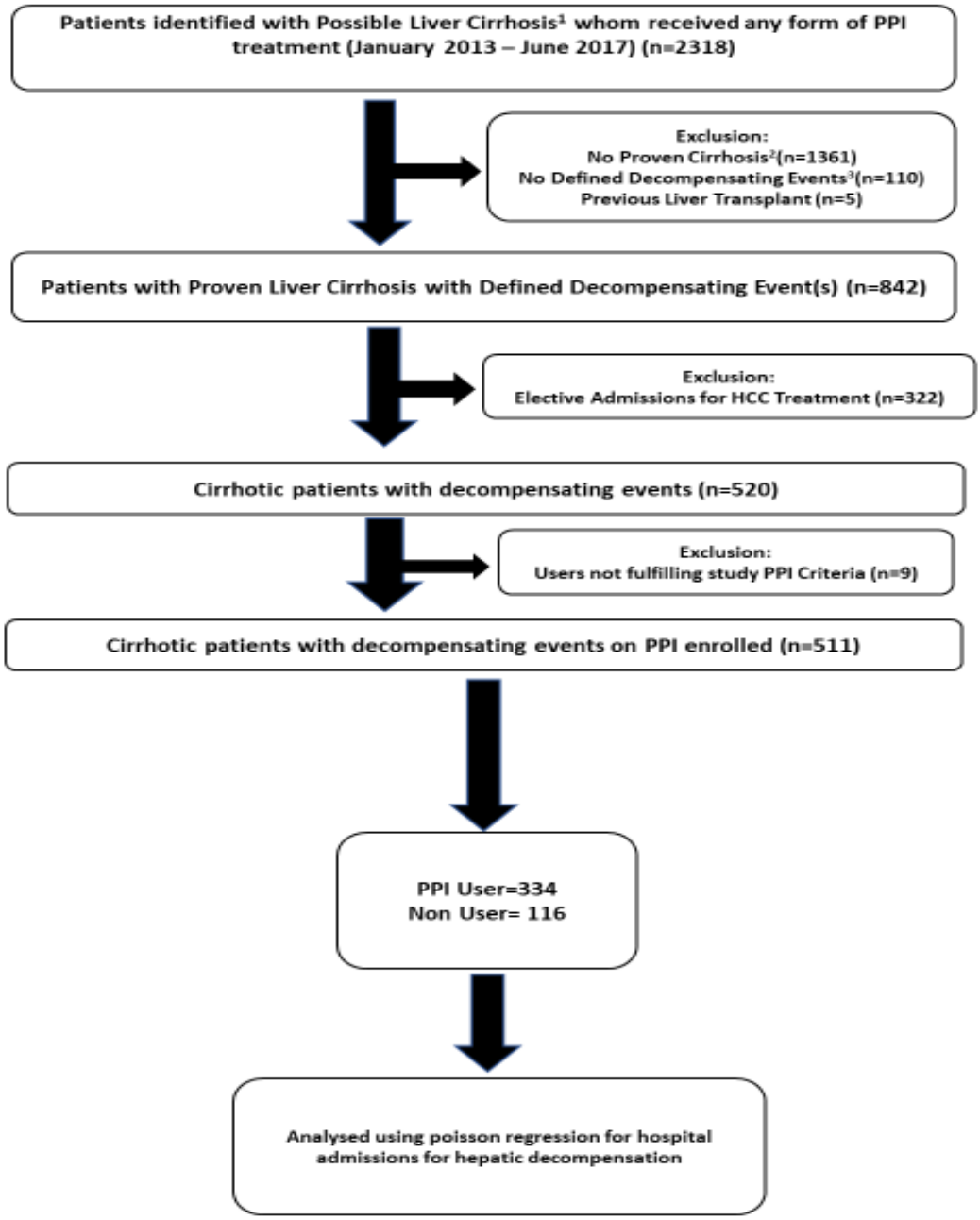
	Direct Acting Antivirals (DAA)[2] Sofosbuvir Daclatasvir Ribavirin Ledipasvir *[2]Available DAAs in Singapore during study period*
Antibiotics (SBP prophylaxis) [3]	Ciprofloxacin *[3]Norfloxacin was not available in Government Restructured Hospitals in Singapore.* *Rifaximin was not available in Singapore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

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: 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 (69.5%)	0.66
Female			
Age (years)	63.1 ± 13.4	64.9 ± 13.0	0.21
Race			0.82
Chinese	75 (64.7%)	200 (59.9%)	
Malay	19 (16.4%)	66 (19.8%)	
Indian	13 (11.2%)	41 (12.3%)	
Others	9 (7.8%)	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 (32.0%)	
Autoimmune	6 (5.2%)	8 (2.4%)	
Others	16 (13.8%)	41 (12.3%)	
Index Hepatic Event:			
HCC	27(23.3%)	44(13.2%)	0.01
Ascites	78 (67.2%)	187 (56.0%)	0.03
SBP	12(10.3%)	25(7.5%)	0.33
HE	27(23.3%)	80(24.0%)	0.88
Variceal Bleed	15(12.9%)	72(21.6%)	0.04
Prevoius 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 (± 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
DM[1]			
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%)	
Malignancy[1]			
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

Supplementary Table 4: 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)	*p-value*
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 ≥ 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: Hepatocelllar Carcinoma

CI: Confidence Interval