Hepatic Failure Associated with Immune Checkpoint Inhibitors: A Real-world Study from the Food and Drug Administration Adverse Event Reporting System (FAERS) Database

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Supplementary Information

Abbreviations:

AIH: autoimmune hepatitis

CI: confidence interval

CTLA-4: cytotoxic T lymphocyte associated protein 4

DEMO: demographic and administrative information

DRUG: drug information

FAERS: Food and Drug Administration Adverse Event Reporting System

ICIs: immune checkpoint inhibitors

IC: information component

IC_{025}: the lower limit of the 95% two-sided confidence interval of the IC

INDI: indications for use

MedDRA: Medical Dictionary for Regulatory Activities

OUTC: patient outcomes

PD-1: programmed cell death protein 1

PD-L1: programmed cell death 1 ligand 1

PTs: preferred terms

REAC: preferred terms coded for the adverse event

ROR: reporting odds ratio

ROR_{025}: the lower limit of the 95% two-sided confidence interval of the ROR

RPSR: report sources

SMQ: Standardised MedDRA Queries

SRS: spontaneous reporting system

THER: therapy start dates and end dates for reported drugs

TTO: time to onset

Table S1 Drug information for 8 FDA approved ICIs

Generic names	Brand names	Approval year	Target
Nivolumab	Opdivo,BMS-986298,Opdyta,BMS-936558	2014	PD-1
Pembrolizumab	Keytruda,MK-3475	2014	PD-1
Cemiplimab	Libtayo,SAR439684,REGN2810	2018	PD-1
Atezolizumab	Tecentriq,MPDL3280A	2016	PD-L1
Avelumab	Bavencio,MSB0010718C	2017	PD-L1
Durvalumab	Imfinzi,MEDI4736	2017	PD-L1
Ipilimumab	Yervoy,BMS-734016	2011	CTLA-4
Tremelimumab	Ticilmumab	-	CTLA-4

Table S2 Summary of major algorithms used for signal detection

Algorithms	Equation*	Criteria
ROR	$ROR= (a/b)/ (c/d)$ $95\%CI=e^{\ln (ROR)\pm 1.96 (1/a+1/b+1/c+1/d)^{0.5}}$	$ROR_{025}>1,N\geq 3$
BCPNN	$IC=\log_2 a (a+b+c+d)/ ((a+c) (a+b))$ $IC_{025}=e^{\ln (IC)-1.96 (1/a+1/b+1/c+1/d)^{0.5}}$	$IC_{025}>0$

BCPNN, Bayesian confidence propagation neural network; CI, confidence interval; IC, information component; IC_{025}, the lower limit of the 95% two-sided CI of the IC; N, the number of co-occurrences; ROR, reporting odds ratio; ROR_{025}, the lower limit of the 95% two-sided CI of the ROR; *a: number of reports containing both the suspect drug and the suspect adverse drug reaction; b: number of reports containing both the suspect drug and other adverse drug reactions (except the event of interest); c: number of reports containing both other medications (except the drug of interest) and the suspect adverse drug reaction; d: number of reports containing other medications and other adverse drug reactions.

Table S3 Number of death cases and fatality proportion of ICI-associated hepatic failure

ICI regimens	Fatality proportion	
	N	%
Monotherapy		
Anti-PD-1	325	68.42%
Nivolumab	235	69.32%
Pembrolizumab	91	65.94%
Cemiplimab	1	100.00%
Anti-PD-L1	109	68.99%
Atezolizumab	88	66.17%
Avelumab	8	88.89%
Durvalumab	14	77.78%
Anti-CTLA-4	95	61.69%
Ipilimumab	93	61.59%
Tremelimumab	2	66.67%
Combination therapy		
Nivolumab+Ipilimumab	76	59.84%
Durvalumab+Tremelimumab	2	66.67%
All Drug	449	68.65%

Table S4 Signals of ICI-associated hepatic failure in the different subgroups of genders and ages

Groups (ICIs vs. all other drugs)	a (N)	b	c	d	ROR (ROR_{025}-ROR_{975})	IC (IC_{025}-IC_{975})
All ICIs	654	119736	17800	9509397	2.92 (2.70-3.16)	1.51 (1.39-1.63)
Gender						
Female	218	40214	8024	5061242	3.42 (2.99-3.91)	1.74 (1.52-1.99)
Male	382	65361	6906	3277610	2.77 (2.50-3.08)	1.42 (1.28-1.57)
Age						
＜65	274	37397	8980	3323999	2.71 (2.40-3.06)	1.41 (1.25-1.59)
≥65	251	46106	3795	1973244	2.83 (2.49-3.22)	1.44 (1.26-1.63)

a: number of reports containing both the ICIs and hepatic failure; b: number of reports containing both the ICIs and all other adverse events (except hepatic failure); c: number of reports containing both all other drugs (except ICIs) and hepatic failure; d: number of reports containing all other drugs and all other adverse events.

CI: confidence interval; IC: information component; IC_{025}: the lower limit of the 95% two-sided confidence interval of the IC; IC_{075}: the upper limit of the 95% two-sided confidence interval of the IC; ROR: reporting odds ratio; ROR_{025}: the lower limit of the 95% two-sided confidence interval of the ROR; ROR_{075}: the upper limit of the 95% two-sided confidence interval of the ROR.

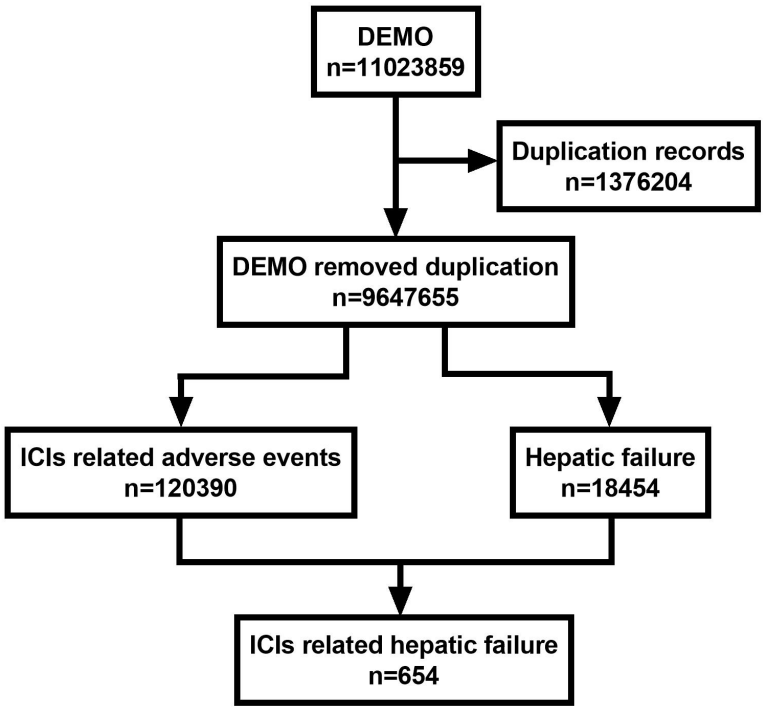

Fig. S1 Process of selecting cases of ICI-associated hepatic failure from the FAERS database

DEMO: demographic and administrative information; FAERS: Food and Drug Administration Adverse Event Reporting System; ICIs: immune checkpoint inhibitors.

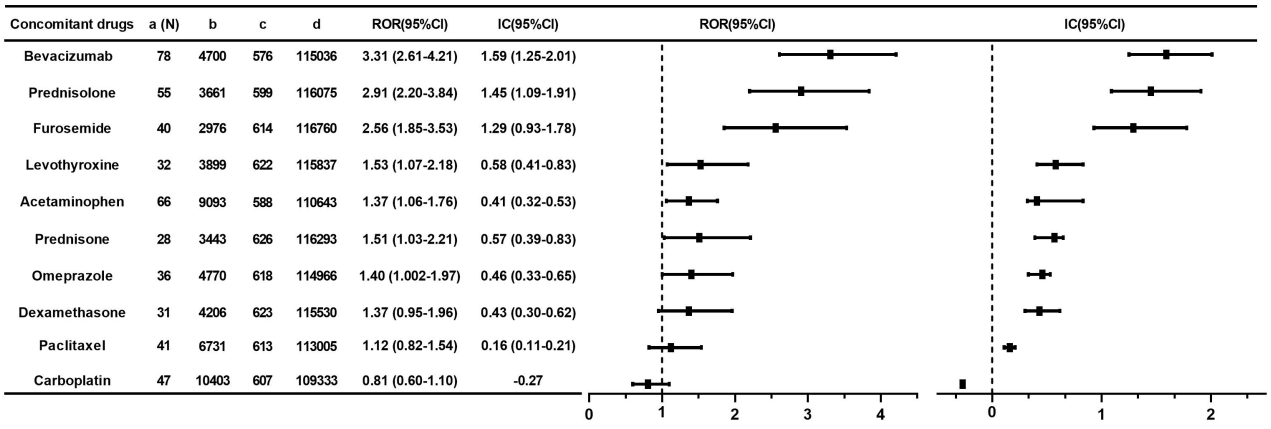

Fig. S2 Signals of concomitant used ICIs with other agents associated hepatic failure

a: number of reports containing both the specific combination regimen and hepatic failure; b: number of reports containing both the specific combination regimen and all other adverse events (except hepatic failure); c: number of reports containing both the specific ICI monotherapy and hepatic failure; d: number of reports containing the specific ICI monotherapy and all other adverse events.

95% CI: the 95% two-sided confidence interval; IC: information component; ROR: reporting odds ratio.