

Table S1. The details of bulk RNA sequencing datasets.

Datasets	Attributes	Sample composition and groups	Reasons for sample exclusion
GSE65682	Training	475 sepsis patients with exact 28-day survival status and specific survival time; 42 healthy controls.	Without prognostic information, or the information was contradictory (GSM1692149, GSM1692379, GSM1602888 and GSM1602942).
GSE57065	Verification	28 sepsis patients; 25 healthy controls.	Repeated sampling
GSE95233	Verification	51 sepsis patients; 22 healthy controls.	Repeated sampling
GSE131761	Verification	114 sepsis patients; 15 healthy controls.	-
GES134347	Verification	156 sepsis patients; 83 healthy controls.	-

Table S2. The inclusion and exclusion criteria of the clinical trial.

Criteria	Groups	Details
Inclusion	Sepsis	1. From the Department of Critical Care Medicine
		2. diagnosed per Sepsis-3 criteria
		3. The same day admitted to the Department of Critical Care Medicine
	Healthy	1. From the Medical Examination Center
		2. On the same day of medical examination
Exclusion	Both	1. Less than 18 years old
		2. Receiving immunosuppressive therapy in the past six months
		3. Immune dysfunction state
		4. Receiving gastrointestinal surgery in the past six months
		5. Inflammatory bowel disease
		6. Severe organ dysfunction
		7. Massive blood transfusion
		8. Pregnancy status or perinatal period

Table S3. The primers used in RT-qPCR.

Genes	Forward primers	Reverse primers
HLA-DPA1	ATGCGCCCTGAAGACAGAATG	ACACATGGTCCGCCTTGATG
ITGB7	CCATTCAGCTTTCACCATGTGC	ACCTTCAGGCGAGTCCAGATT
CXCR4	ACGCCACCAACAGTCAGAG	AGTCGGAATAGTCAGCAGGA
ANKRD55	AACATGCAGGATGCTTATGGC	TGGCACCGTTTCTGAGTAGAC
CX3CR1	GTGTCACCGACATTTACCTCC	AAGGCGGTAGTGAATTTGCAC
GIMAP4	AACTTGTCGTAGTTGACACACC	GCGAATAATCTCCTTGGACGTTT
GAPDH	ACAACCTTTGGTATCGTGGAAGG	GCCATCACGCCACAGTTTC

RT-qPCR, Real-Time Quantitative Polymerase Chain Reaction.

Table S4. The data source of the MR study.

Exposures/Outcomes	Traits	GWAS IDs
HLA-DPA1	ENSG00000231389	eqtl-a-ENSG00000231389
ITGB7	ENSG00000139626	eqtl-a-ENSG00000139626
CXCR4	ENSG00000121966	eqtl-a-ENSG00000121966
ANKRD55	ENSG00000164512	eqtl-a-ENSG00000164512
CX3CR1	ENSG00000168329	eqtl-a-ENSG00000168329
GIMAP4	ENSG00000133574	eqtl-a-ENSG00000133574
Sepsis	Sepsis	ieu-b-69
Sepsis mortality	Sepsis (28-day death in critical care)	ieu-b-4981

MR, Mendelian Randomization.

Table S5. The IVs used in the MR study.

Exposures	Outcomes	SNP	effect_allele. exposure	other_allele. exposure	effect_allele. outcome	other_allele. outcome	beta. exposure	beta. outcome	eaf. exposure	eaf. outcome	palindromic	ambiguous	chr	pos	se.outcome	samplesize. outcome	pval. outcome	pval. exposure	pos. exposure	se. exposure	chr. exposure	samplesize. exposure	FSTAT
HLA-DPA1	Sepsis	rs11204677	G	C	G	C	-0.054569	-0.007879	0.526418	0.553023	TRUE	TRUE	1	150574695	0.0142648	462918	0.53	4.62E-06	150574695	0.0119113	1	13006	20.99
HLA-DPA2	Sepsis	rs114390018	T	C	T	C	-0.739853	-0.017702	0.145242	0.175298	FALSE	FALSE	6	33029384	0.0187954	462918	0.34	1.00E-200	33029384	0.015702	6	9175	2219.66
HLA-DPA3	Sepsis	rs13203715	G	A	G	A	-0.389618	0.0330122	0.121006	0.114275	FALSE	FALSE	6	32988588	0.022271	462918	0.22	1.92E-104	32988588	0.0179523	6	7572	470.89
HLA-DPA4	Sepsis	rs13330176	A	T	A	T	-0.105538	0.0229334	0.21644	0.237962	TRUE	FALSE	16	86019087	0.0167907	462918	0.11	2.55E-13	86019087	0.0144251	16	13344	53.52
HLA-DPA5	Sepsis	rs17658229	C	T	C	T	-0.128883	0.0486155	0.0437999	0.047997	FALSE	FALSE	5	172191052	0.0334019	462918	0.16	9.22E-06	172191052	0.0290624	5	13344	19.66
HLA-DPA6	Sepsis	rs2857218	G	C	G	C	-0.05756	0.0100599	0.375694	0.389578	TRUE	FALSE	6	32855340	0.0145417	462918	0.51	2.77E-06	32855340	0.0122798	6	6458	21.96
HLA-DPA7	Sepsis	rs386879	A	T	A	T	0.107118	0.0009337	0.294243	0.346631	TRUE	FALSE	6	33506733	0.0149207	462918	0.52	2.01E-16	33506733	0.0130295	6	13340	67.58
HLA-DPA8	Sepsis	rs4705862	T	A	T	A	-0.055897	-0.006334	0.440695	0.431128	TRUE	TRUE	5	131813219	0.0143961	462918	0.56	3.07E-06	131813219	0.0119789	5	13344	21.77
HLA-DPA9	Sepsis	rs7944584	T	A	T	A	0.0651286	-0.005865	0.268509	0.276922	TRUE	FALSE	11	47336320	0.0158623	462918	0.630001	1.21E-06	47336320	0.0134183	11	13344	23.56
HLA-DPA10	Sepsis	rs8026803	C	T	C	T	-0.067733	-0.031805	0.247924	0.260493	FALSE	FALSE	15	80260014	0.0161536	462918	0.0929994	8.73E-07	80260014	0.0137715	15	13344	24.19
ITGB7	Sepsis	rs10423726	A	C	A	C	-0.123182	-0.011485	0.595533	0.58069	FALSE	FALSE	19	16444697	0.0151179	462918	0.27	0.0120825	16444697	14496	19	2.09E-24	103.93
ITGB8	Sepsis	rs11170231	A	G	A	G	0.10707	0.0250054	0.161433	0.15309	FALSE	FALSE	12	53068633	0.0199129	462918	0.4	0.0161512	53068633	31355	12	3.38E-11	43.94
ITGB9	Sepsis	rs11653357	A	G	A	G	-0.075936	-0.013067	0.17703	0.175134	FALSE	FALSE	17	33923607	0.0186474	462918	0.39	0.0155799	33923607	31270	17	1.09E-06	23.75
ITGB10	Sepsis	rs1354034	C	T	C	T	-0.056313	0.0312447	0.618137	0.599112	FALSE	FALSE	3	56849749	0.0144583	462918	0.02	0.0122412	56849749	31470	3	4.22E-06	21.16
ITGB11	Sepsis	rs2280696	T	A	T	A	0.801045	0.0307945	0.0817348	0.056764	TRUE	FALSE	12	53512756	0.0306528	462918	0.44	0.0206521	53512756	31135	12	1.00E-200	1504.38
ITGB12	Sepsis	rs74088990	G	A	G	A	0.844415	0.0282628	0.0245041	0.031009	FALSE	FALSE	12	53593445	0.0414491	462918	0.5	0.0378339	53593445	26388	12	2.42E-110	498.10
ITGB13	Sepsis	rs9420589	T	G	T	G	-0.059749	-0.015622	0.428682	0.433552	FALSE	FALSE	10	94450233	0.0143365	462918	0.23	0.0120159	94450233	31270	10	6.61E-07	24.72
CXCR4	Sepsis	rs10098310	A	G	A	G	0.064501	0.0074328	0.575007	0.570067	FALSE	FALSE	8	130613614	0.0144323	462918	0.44	8.19E-08	31355	130613614	0.0120275	8	28.76
CXCR5	Sepsis	rs11897084	G	A	G	A	0.0791658	0.0332864	0.538148	0.558763	FALSE	FALSE	2	136861225	0.0143517	462918	0.012	3.10E-11	31468	136861225	0.0119197	2	44.11
CXCR6	Sepsis	rs56388170	T	G	T	G	-0.084325	-0.010373	0.289189	0.2928	FALSE	FALSE	7	28724374	0.0157155	462918	0.47	1.25E-10	31141	28724374	0.0131081	7	41.38
ANKRD55	Sepsis mortality	rs1040555	T	A	T	A	0.0586246	-0.107567	0.451876	0.444514	TRUE	TRUE	20	31380201	0.0795846	431365	0.176503	0.0119488	20	9.29E-07	31355	31380201	24.07
ANKRD56	Sepsis mortality	rs112861549	G	A	G	A	0.301594	0.254141	0.0323343	0.0360886	FALSE	FALSE	5	55134598	0.213189	431365	0.233224	0.0335514	5	2.50E-19	30252	55134598	80.80
ANKRD57	Sepsis mortality	rs11649653	G	C	G	C	0.0791747	0.0142496	0.393125	0.382613	TRUE	FALSE	16	30918487	0.0803932	431365	0.859313	0.0121669	16	7.66E-11	30757	30918487	42.34
ANKRD58	Sepsis mortality	rs11920354	A	C	A	C	-0.075343	-0.097901	0.372903	0.388519	FALSE	FALSE	3	47262246	0.0804619	431365	0.223704	0.0122914	3	8.80E-10	28703	47262246	37.57
ANKRD59	Sepsis mortality	rs12044149	T	G	T	G	-0.063226	-0.135292	0.252725	0.254585	FALSE	FALSE	1	67600686	0.0900253	431365	0.132886	0.0136852	1	3.84E-06	31469	67600686	21.34
ANKRD60	Sepsis mortality	rs13062095	C	T	C	T	-0.057412	-0.044348	0.350092	0.336096	FALSE	FALSE	3	101267385	0.0836039	431365	0.595795	0.0124681	3	4.13E-06	31355	101267385	21.20
ANKRD61	Sepsis mortality	rs13163043	G	A	G	A	-0.372751	-0.087153	0.0309123	0.0381432	FALSE	FALSE	5	55579422	0.204333	431365	0.669726	0.0342438	5	1.35E-27	28088	55579422	118.48
ANKRD62	Sepsis mortality	rs138752204	G	A	G	A	0.394997	0.142137	0.0169951	0.017454	FALSE	FALSE	5	55102584	0.311619	431365	0.6483	0.0459272	5	7.94E-18	24602	55102584	73.96
ANKRD63	Sepsis mortality	rs141453671	T	C	T	C	-0.390461	0.0279633	0.0347493	0.0409042	FALSE	FALSE	5	55517699	0.206323	431365	0.892192	0.032331	5	1.40E-33	29437	55517699	145.84
ANKRD64	Sepsis mortality	rs146345203	A	C	A	C	-0.272648	-0.192704	0.0271935	0.0311643	FALSE	FALSE	5	55630755	0.227811	431365	0.397613	0.0365211	5	8.29E-14	29058	55630755	55.73
ANKRD65	Sepsis mortality	rs147231428	G	A	G	A	-0.383156	0.392549	0.0146409	0.0084699	FALSE	FALSE	5	55555585	0.426328	431365	0.357172	0.0494472	5	9.28E-15	21834	55555585	60.04
ANKRD66	Sepsis mortality	rs2609255	T	G	T	G	0.0624272	-0.121931	0.760626	0.787116	FALSE	FALSE	4	89811195	0.0961233	431365	0.204623	0.0139384	4	7.51E-06	31470	89811195	20.06
ANKRD67	Sepsis mortality	rs3184504	C	T	C	T	-0.078405	0.0239425	0.542056	0.517667	FALSE	FALSE	12	111884608	0.0788562	431365	0.761416	0.0119276	12	4.91E-11	28204	111884608	43.21
ANKRD68	Sepsis mortality	rs3774959	A	G	A	G	0.126657	-0.085433	0.352643	0.372497	FALSE	FALSE	4	103511114	0.0815151	431365	0.294608	0.0124111	4	1.88E-24	31355	103511114	104.14
ANKRD69	Sepsis mortality	rs62359589	T	C	T	C	-0.200409	-0.029808	0.0349461	0.0355449	FALSE	FALSE	5	54839646	0.212326	431365	0.888352	0.0323654	5	5.93E-10	25550	54839646	38.34
ANKRD70	Sepsis mortality	rs6457374	T	C	T	C	-0.091439	-0.047403	0.754006	0.70412	FALSE	FALSE	6	31272261	0.0865871	431365	0.584059	0.0137981	6	3.43E-11	30389	31272261	43.91
ANKRD71	Sepsis mortality	rs6873385	A	T	A	T	-0.718993	0.0610851	0.195603	0.205847	TRUE	FALSE	5	55436851	0.0980869	431365	0.533439	0.0137299	5	1.00E-200	25941	55436851	2742.09
ANKRD72	Sepsis mortality	rs6890853	A	G	A	G	0.0632219	-0.048003	0.27143	0.279205	FALSE	FALSE	5	35852311	0.0875065	431365	0.583307	0.0133732	5	2.27E-06	31355	35852311	22.35
ANKRD73	Sepsis mortality	rs7090504	A	T	A	T	0.0678845	-0.051848	0.204318	0.20099	TRUE	FALSE	10	6091017	0.0984669	431365	0.598501	0.0147501	10	4.18E-06	31470	6091017	21.18
ANKRD74	Sepsis mortality	rs72752253	T	C	T	C	0.263669	-0.067221	0.0233297	0.0276445	FALSE	FALSE	5	55647811	0.238578	431365	0.778132	0.0393665	5	2.12E-11	28929	55647811	44.86
ANKRD75	Sepsis mortality	rs72928038	A	G	A	G	-0.117706	-0.153033	0.158151	0.17888	FALSE	FALSE	6	90976768	0.102723	431365	0.136285	0.0162813	6	4.84E-13	28899	90976768	52.26
ANKRD76	Sepsis mortality	rs78157088	G	A	G	A	0.184571	0.184647	0.0233865	0.0209667	FALSE	FALSE	5	55660376	0.275322	431365	0.502439	0.0393516	5	2.73E-06	29234	55660376	22.00
ANKRD77	Sepsis mortality	rs8078723	C	T	C	T	-0.0714	-0.074819	0.379928	0.386449	FALSE	FALSE	17	38166879	0.0806701	431365	0.353682	0.0122476	17	5.55E-09	31470	38166879	33.98
ANKRD78	Sepsis mortality	rs917116	G	T	G	T	-0.14661	0.0072217	0.250264	0.213161	FALSE	FALSE	7	28172739	0.0956594	431365	0.939822	0.0136846	7	8.79E-27	31355	28172739	114.77
ANKRD79	Sepsis mortality	rs934734	A	G	A	G	-0.055674	-0.141676	0.52687	0.493921	FALSE	FALSE	2	65595586	0.0782764	431365	0.070304	0.0119115	2	2.95E-06	30971	65595586	21.84
ANKRD80	Sepsis mortality	rs9525625	C	T	C	T	0.0740444	-0.080441	0.522329	0.528342	FALSE	FALSE	13	43018030	0.0788814	431365	0.307834	0.0118991	13	4.88E-10	31355	43018030	38.72
CX3CR1	Sepsis mortality	rs10732976	A	G	A	G	-0.063266	-0.032057	0.704724	0.695854	FALSE	FALSE	1	185409061	0.0858752	431365	0.708928	1.22E-06	1	0.0130364	30780	185409061	23.55
CX3CR2	Sepsis mortality	rs11711752	G	A	G	A	0.282659	-0.069241	0.915285	0.915994	FALSE	FALSE	3	39294618	0.143138	431365	0.628575	2.10E-40	3	0.0212412	30769	39294618	177.07
CX3CR3	Sepsis mortality	rs1354034	C	T	C	T	-0.080547	-0.057012	0.618137	0.598138	FALSE	FALSE	3	56849749	0.0800281	431365	0.476218	4.55E-11	3	0.0122316	30895	56849749	43.36
CX3CR4	Sepsis mortality	rs55908509	A	G	A	G	-0.106195	0.0956827	0.3284	0.327732	FALSE	FALSE	19	16442019	0.0834993	431365	0.251833	4.44E-17	19	0.0126417	21915	16442019	70.56
CX3CR5																							

Table S6. The main results of the MR study.

Exposures	Outcomes	Number of SNPs	Methods	OR (95% CI)	P value
HLA-DPA1	Sepsis	10	IVW	1.00 (0.95, 1.05)	0.921
		10	MR Egger	1.01 (0.94, 1.08)	0.867
		10	Weighted median	1.02 (0.97, 1.07)	0.418
		10	Weighted mode	1.01 (0.96, 1.06)	0.757
ITGB7	Sepsis	7	IVW	1.04 (0.98, 1.11)	0.195
		7	MR Egger	1.04 (0.96, 1.13)	0.383
		7	Weighted median	1.04 (0.98, 1.10)	0.227
		7	Weighted mode	1.04 (0.98, 1.10)	0.245
CXCR4	Sepsis	3	IVW	1.27 (1.02, 1.58)	0.036
		3	MR Egger	1.79 (0.15, 22.02)	0.729
		3	Weighted median	1.18 (0.89, 1.55)	0.246
		3	Weighted mode	1.13 (0.78, 1.62)	0.583
ANKRD55	Sepsis mortality	26	IVW	1.00 (0.81, 1.24)	0.981
		26	MR Egger	0.93 (0.71, 1.24)	0.64
		26	Weighted median	0.92 (0.71, 1.19)	0.528
		26	Weighted mode	0.95 (0.73, 1.23)	0.703
CX3CR1	Sepsis mortality	8	IVW	0.84 (0.56, 1.25)	0.382
		8	MR Egger	0.61 (0.33, 1.11)	0.154
		8	Weighted median	0.81 (0.50, 1.32)	0.396
		8	Weighted mode	0.76 (0.47, 1.23)	0.309
GIMAP	Sepsis mortality	9	IVW	0.76 (0.60, 0.98)	0.032
		9	MR Egger	0.86 (0.63, 1.19)	0.400
		9	Weighted median	0.79 (0.61, 1.03)	0.080
		9	Weighted mode	0.79 (0.61, 1.03)	0.122

MR, Mendelian Randomization; IVW, Inverse-Variance Weighted.

Table S7. The heterogeneity, pleiotropy and direction analyses of the MR study.

Exposures	Outcomes	Heterogeneity (IVW)		Heterogeneity (MR Egger)		Pleiotropy		Direction	
		Q statistic	P value	Q statistic	P value	Egger Intercept	P value	SNP_r <sup>2</sup> (Exposure)	SNP_r <sup>2</sup> (Outcome)
HLA-DPA1	Sepsis	12.0	0.211	12.0	0.151	-0.001	0.875	0.176	2.5E-05
ITGB7	Sepsis	7.8	0.254	7.8	0.168	0.000	0.981	0.058	2.28E-05
CXCR4	Sepsis	1.7	0.429	1.6	0.209	-0.026	0.832	0.004	1.6E-05
ANKRD55	Sepsis mortality	21.3	0.677	20.7	0.655	0.020	0.458	0.080	4.93E-05
CX3CR1	Sepsis mortality	6.6	0.469	4.6	0.590	0.072	0.209	0.033	1.71E-05
GIMAP4	Sepsis mortality	5.4	0.711	3.9	0.787	-0.097	0.261	0.054	2.32E-05

MR, Mendelian Randomization.