eTable 1. Patient characteristics in the included studies

Source	**Patients[a] (total/itvn/std), *n***	**Age (years)** Mean (SD)		**Sex** (% men)		**Illness Severity Score**	
		Intervention	**Standard**	**Intervention**	**Standard**	**Intervention**	**Standard**
Al-Asadi et al. 1996 (retrospective)	2409/1005/1404	NR	NR	NR	NR	NR	NR
Al-Asadi et al. 1996 (prospective)	2664/1005/1659	NR	NR	NR	NR	NR	NR
Baldock et al. 2001	744/387/357	59	57	61	52	NR	NR
Blunt and Burchett 2000	721/393/328	61 (2.9)[b]	60 (2.7)[b]	NR	NR	APACHE II 19 (1.2)	APACHE II 18 (1.1)
Brown and Sullivan 1989	439/216/223	NR	NR	NR	NR	APACHE II 18 (8.2)	APACHE II 19 (9.1)
Carson et al. 1996	245/121/124	53 (19)	59 (18)	NR	NR	APACHE II 21 (8.6)	APACHE II 15 (8.3)
DiCosmo 1999	2959/1292/1667	NR	NR	NR	NR	NR	NR
Dimick et al. 2001	351/182/169	59 (12)	62 (12)	73	79	NR	NR
Dimick et al. 2002	551/276/275	56 (15)	58 (16)	83	67	NR	NR
Gajic et al. 2008	2622/1321/1301	69 (18)[b]	69 (17)[b]	54	56	APACHE III 62 (22)[b]	APACHE III 63 (25)[b]
Gannon et al. 2010	2948/1659/1289	NR	NR	NR	NR	NR	NR
Garland et al. 1996	106/32/74	NR	NR	NR	NR	APACHE II 26.1 (20.7)	APACHE II 24.3 (21.7)
Garland et al. 2012	501/244/257	59.3 (17)[b]	58.3 (17)[b]	55	55	APACHE II 17.6 (7.3)	APACHE II 19.2 (8.1)
Ghorra et al. 1999	274/149/125	66 (1.2)	67 (1.4)	53	63	APACHE III 36	APACHE III 39

Goh et al. 2001	619/355/264	1 (8)[b]	0.3 (8)[b]	NR	NR	PRISM II 12 (26)	PRISM II 9.0 (23)
Hansen et al. 1999	198/100/98	59 (1.3)	61 (1.5)	60	56	APACHE II 12 (0.4)	APACHE II 14 (0.5)
Hawari et al. 2009	1070/834/236	56	54	58	59	APACHE II 21 (7.1)	APACHE II 21 (8.5)
Kim et al. 2012	830/157/673	64 (19)	61 (18)	60	64	16 (10)	20 (10)
Kim JH et al. 2012	251/78/173	67 (13)	65 (13)	69	58	APACHEII 26 (8)	APACHEII 20(9)
Kumar et al. 2009	1866/933/933	65 (11)	65 (11)	75	74	APACHE II 14 (4.8)	APACHE II 15 (4.1)
Kuo et al. 2000	667/491/176	66 (23)	63 (16)	NR	NR	NR	NR
Lettieri et al. 2009	965/223/742	33 (6.1)	34 (7.7)	91	94	NR	NR
Levy et al. 2008	24731/18618/22870	64[c]	60[c]	52[c]	54[c]	SAPS II[c] 13.7	SAPS II[c] 16.5
Lin et al. 2008	280/185/95	NR	NR	NR	NR	NR	NR
Marini et al. 1995	292/227/65	69 (1.3)	72 (1.0)	NR	NR	APACHE II 15 (0.7)	APACHE II 14 (1.2)
McMillen et al. 2012	9239/3429/5810	NR	NR	NR	NR	NR	NR
Multz et al. 1998 (retrospective)	280/185/95	63 (1.4)	64 (1.8)	52	52	NR	NR
Multz et al. 1998 (prospective)	306/154/152	61 (1.4)	62 (1.5)	48	60	NR	NR
Nathens et al. 2006	6789/5228/1561	NR	NR	72	69	NR	NR
Netzer et al. 2011	3687/2424/1263	54 (16)	53 (16)	45	45	CMI score 2 (1.6)[b] MICU	CMI score 2 (1.6)[b] MICU

						Charlson score 2 (2.2)[b]	Charlson score 2 (2.2)[b]
Nishisaki et al. 2012	18702/8520/10182	5.5 (8.8)[b]	6 (8.7)[b]	59	58	PRISM II 4.3 (6.4)	PRISM II 4.7 (6.8)
Petitti et al. 2012	13378/1979/11399	43 (20)	37 (18)	71	66	NR	NR
Pollack et al. 1988	262/113/149	1.6	1	50	56	NR	NR
Pollack et al. 1994	4845/2036/2809	NR	NR	NR	NR	NR	NR
Pronovost et al. 1999	2606/2134/472	NR	NR	NR	NR	NR	NR
Reich et al. 1998	1656/830/826	NR	NR	NR	NR	NR	NR
Reriani et al. 2012	3281/1697/1584	66 (22)[b]	67 (20)[b]	52	55	37 (19)[b]	30 (21)[b]
Resnick et al. 2010	470/245/225	0.6 (0.1)	0.6 (0.1)	56	52	NR	NR
Reynolds et al. 1988	212/112/100	56 (19)	57 (19)	NR	NR	APACHE II 28 (10)	APACHE II 29 (11)
Rivera et al. 2009	220/115/105	67	67	NR	NR	APACHE II 9.1	APACHE II 7.8
Roberts et al. 2008	4705/890/3815	NR	NR	NR	NR	NR	NR
Sales et al. 2011	34093/21287/12806	NR	NR	NR	NR	NR	NR
Samuels et al. 2011	703/386/317	53 (14)	51 (13)	31	30	NR	NR
Singh et al. 2008	94/50/44	NR	NR	NR	NR	NR	NR
Suarez et al. 2004	2381/1180/1201	60 (17)	59 (18)	49	48	APACHE III 36	APACHE III 36
Treggiari et al. 2007	1075/684/391	57 (18)	66 (16)	64	56	APACHEIII 87 (33.9)	APACHEIII 88 (31.3)
Thurlby et al. 2005	533/471/62	NR	NR	NR	NR	NR	NR
Topeli et al. 2005	559/359/200	NR	NR	NR	NR	APACHE II	APACHE II

						20 (8.9)	13 (6.7)
Varelas et al. 2004	2366/1279/1087	52 (19)	52 (19)	56	58	NR	NR
Wallace et al. 2012	65752/14424/51328	62 (17.1)[b]	66 (16.3)[b]	55	58	APS 38 (23.0)[b]	APS 36 (21.5)[b]
Wise et al. 2012	1356/528/828	61 (16)	61 (18)	49	48	SAPSII 45 (17)	SAPSII 37 (15)
Zwaal and Baba 2004	1372/819/553	NR	NR	NR	NR	APACHE 14.4	APACHE 16.4

Of the 246481 patients enrolled, 101797 were enrolled in a higher-intensity arm. [a]The number of patients in each category corresponds to the number used in the meta-analysis. Continuous data are expressed as mean (SD).[b]Medians reported instead of means. [c]Mean of largest patient grouping (>98% of group).

APACHE, Acute Physiology and Chronic Health Evaluation; APS, Acute Physiology Score; CMI, Case Mix Index; ICU, Intensive Care Unit; NR, Not reported; PRISM, Pediatric Risk of Mortality Score; SAPS, Simplified Acute Physiology Score.

See main text for reference numbers.

eTable 2: Study quality assessment as per Newcastle-Ottawa Score of studies included for systematic review

Source	Selection (4)	Comparability (2)	Outcome (3)	Total (9)
Al-Asadi et al. 1996 (prospective)	4	0	2	5
Al-Asadi et al. 1996 (retrospective)	4	1	2	7
Baldock et al. 2001	4	1	3	8
Blunt and Burchett 2000	4	1	2	7
Brown and Sullivan 1989	4	0	3	7
Carson et al. 1996	4	1	3	8
DiCosmo 1999	4	1	2	7
Dimick et al. 2001	4	1	2	7
Dimick et al. 2002	4	1	2	7
Gajic et al. 2008	4	2	2	8
Gannon et al. 2010	4	0	2	6
Garland et al. 1996	4	2	2	8
Garland et al. 2012	4	2	2	8
Ghorra et al. 1999	4	1	2	7
Goh et al. 2001	4	1	2	7
Hansen et al. 1999	4	1	2	7
Hawari et al. 2009	4	1	2	7
Kumar et al. 2009	4	1	2	7
Kuo et al. 2000	4	1	3	8
Lettieri et al. 2009	4	1	2	7
Levy et al. 2008	4	2	2	8
Li et al 1984	4	1	2	7
Lin et al. 2008	4	0	2	5
Marini et al. 1995	4	1	2	7
Multz et al. 1998 (prospective)	4	1	2	7

Multz et al. 1998 (retrospective)	4	1	2	7
Nathens et al. 2006	4	2	2	8
Netzer et al. 2011	4	1	2	7
Nishisaki et al. 2012	4	2	2	8
Pollack et al. 1988	4	1	2	7
Pollack et al. 1994	4	1	2	7
Pronovost et al. 1999	4	1	3	8
Reich et al. 1998	4	1	2	7
Reynolds et al. 1988	4	1	2	7
Rivera et al. 2009	4	1	2	7
Roberts et al. 2008	4	0	2	6
Singh et al. 2008	4	1	2	7
Suarez et al. 2004	4	1	2	7
Treggiari et al. 2007	4	2	2	8
Thurlby et al. 2005	4	0	2	6
Topeli et al. 2005	4	1	2	7
Varelas et al. 2004	4	2	2	8
Zwaal and Baba 2004	4	1	2	7
Wallace et al. 2012	4	2	3	9
McMillen et al. 2012	4	0	2	6
Resnick et al. 2010	4	2	2	8
Reriani et al. 2012	4	2	2	8
Petitti et al. 2012	4	2	2	8
Kim JH et al. 2012	4	2	3	9
Sales et al. 2011	4	1	2	7
Kim et al. 2012	4	2	2	8
Samuels et al. 2011	4	2	2	8
Wise et al. 2012	4	2	2	8

Study quality was assessed using the Newcastle-Ottawa Score. The number in parentheses after the headings of columns 2-5 refers to the maximum possible score. Points for selection are given for representativeness of the exposed cohort, selection of the non-exposed

cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at start of study. Points for comparability are given for comparability of cohorts on the basis of the design or analysis. Points for outcomes are given for assessment of outcome, adequacy of length of follow-up, and adequacy of follow-up.

See main text for reference numbers.

eTable 3: Study quality characteristics including assessment of risk for bias

Source	Risk for Bias due to Temporal Trends	Adjustment for Confounding Variables	Risk for Bias due to Confounding Variables
Al-Asadi et al. 1996 (prospective)	Low	APACHE II	Low
Al-Asadi et al. 1996 (retrospective)	Medium	APACHE II	Low
Baldock et al. 2001	Medium	APACHE II	Low
Blunt and Burchett 2000	NR	APACHE II	Low
Brown and Sullivan 1989	Low	APACHE II	Low
Carson et al. 1996	Low	APACHE II	Low
DiCosmo 1999	Medium	Percentage of patients requiring MV, Case mix index for hospital admissions	Medium
Dimick et al. 2001	Medium	Age, sex, nature of admission, Romano's modification (comorbidity)	Medium
Dimick et al. 2002	Medium	Age, sex, nature of admission, extent of operation, Romano's modification (comorbidity)	Medium
Gajic et al. 2008	Low	APACHE III	Low
Gannon et al. 2010	Low	NR	High
Garland et al. 1996	Low	APACHE II	Low
Garland et al. 2012	Low	APACHE II	Low
Ghorra et al. 1999	Low	APACHE III	Low
Goh et al. 2001	Medium	PRISM II	Low
Hansen et al. 1999	Low	APACHE II	Low

Hawari et al. 2009	Medium	APACHE II	Low
Kim et al. 2012	Low	APACHE II	Low
Kim JH et al. 2012	Low	APACHE II	Low
Kumar et al. 2009	Medium	APACHE II	Low
Kuo et al. 2000	High	APACHE II	Low
Lettieri et al. 2009	Medium	Age, sex, combat-associated injuries	Medium
Levy et al. 2008	NR	NR	NR
Li et al 1984	Low	Age, sex, reason for admission, mental status	Medium
Lin et al. 2008	Low	Age, sex, Charlson comorbidity score	Medium/High
Marini et al. 1995	Low	APACHE II	Low
McMillen et al. 2012	High	NR	High
Multz et al. 1998 (prospective)	Low	MPM	Low
Multz et al. 1998 (retrospective)	Low	MPM	Low
Nathens et al. 2006	Low	Age, sex, race, health insurance status, Charlson comorbidity score	Medium
Netzer et al. 2011	Medium	Age, sex, MICU Charlson comorbidity score, CMI score	Medium
Nishisaki et al. 2010	High	PRISM II	Low
Petitti et al. 2012	High	NR	High
Pollack et al. 1988	Low	PSI	Low
Pollack et al. 1994	Medium	PRISM II	Low
Pronovost et al. 1999	Low	Age, sex, nature of admission, Romano's modification (comorbidity)	Medium

Reich et al. 1998	Low	Nursing hours per day	Medium
Reriani et al. 2012	Low	APACHE III	Low
Resnick et al. 2010	Low	NR	High
Reynolds et al. 1988	Low	APACHE II	Low
Rivera et al. 2009	Low	APACHE II	Low
Roberts et al. 2008	Medium	APACHE II	Low
Sales et al. 2011	Low	Charlson score, Elixhauser score	Low
Samuels et al. 2011	High	Hunt and Hess grade	Medium
Singh et al. 2008	High	SOFA	Low
Suarez et al. 2004	Medium	APACHE III	Low
Treggiari et al. 2007	Low	APACHE III	Low
Thurlby et al. 2005	NR	NR	High
Topeli et al. 2005	High	APACHE II	Low
Varelas et al. 2004	Medium	Age, sex, urgency of admission, payer class	Medium
Wallace et al. 2012	Low	APS	Low
Wise et al. 2012	Low	SAPS II	Low
Zwaal and Baba 2004	Low	APACHE	Low

Risk of bias due to temporal trends is classified as low if study duration was 2 years or less, medium if 2 to 4 years, and high if more than 4 years. Risk of bias from confounding is classified as low if validated physiologic method of risk adjustment was used, medium if selected clinical data were used, and high if no risk adjustment was used. Risk of bias from incomplete follow-up is classified as low if follow-up is 90% to 100% complete, medium if follow-up is 80% to 89%, and high if less than 80%. Risk for bias due to incomplete follow-up was low in all studies(1).

APACHE, Acute Physiology and Chronic Health Evaluation; APS, Acute Physiology Score; CMI, Case Mix Index; ICU, Intensive Care Unit; NR, Not reported; PSI, Physiology Severity Index; PRISM, Pediatric Risk of Mortality Score; SAPS, Simplified Acute Physiology Score.

See main text for reference numbers.

eTable 4. Subgroup analyses for type of ICU, age of study population, or geographical location and hospital mortality

ICU type	**n studies**	**I^2 (%)**	**Risk Ratio (95% CI)**	**p-value test for interaction**
Medical ICUs (2-9)	10	89	1.12 (0.83-1.5)	--
Surgical ICUs (10-13)	4	77	0.84 (0.44-1.6)	0.42
Mixed MSICUs (14-23)	10	35	0.74 (0.66-0.83)	0.02

Population type	**n studies**	**I^2 (%)**	**Risk Ratio (95% CI)**	**p-value test for interaction**
Pediatric (24-26)	3	96	0.74 (0.22-2.5)	--
Adult (2-8,10-23,27-33)	31	97	0.84 (0.70-1.0)	0.84

Geographical location	**n studies**	**I^2 (%)**	**Risk Ratio (95% CI)**	**p-value test for interaction**
United States (2-6,10-12,20-23,25-30,32)	23	98	0.87 (0.70-1.1)	--
United Kingdom (14,15)	2	0	0.68 (0.57-0.81)	0.09
Asia-Pacific (17,24)	2	0	0.40 (0.30-0.52)	<0.001

Decade of publication	**n studies**	I^2 **(%)**	**Risk Ratio (95% CI)**	**p-value test for interaction**
1980-1989 (6,16,25)	3	0	0.74 (0.63-0.87)	--
1990-1999 (2-5,10,11,26,32)	10	87	0.96 (0.69-1.3)	0.16
2000-2009 (7,8,13-15,18,20-24,27-31)	16	98	0.70 (0.54-0.90)	0.72
2010-2012 (9,12,17,19,33)	5	91	1.2 (0.84-1.8)	0.02

Pooled risk ratios were calculated using random-effects models.

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