

Effect of norepinephrine *versus* vasopressin weaning on incidence of hypotension in septic shock patients: a systematic review and meta-analysis

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Table 1S - Literature search strategy details

#	Query	Results from 5 Feb 2024
	ClinicalTrials.gov – *classic site* (2000+)	
	Other terms: (sepsis OR septic) AND (norepinephrine OR noradrenaline) AND (vasopressin OR vasopressins OR vasoactive OR vasoconstrictor OR vasoconstrictors OR vasopressor OR vasopressors)	193
	Cochrane Central Register of Controlled Trials via Ovid (1991+)	
1	(sepsis or septic* or pyemi* or pyaemi* or pyohemi* or bacteremi* or bacteriemi* or bacteraemi* or bacillaemi* or bacillemi* or endotoxemi* or endotoxaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or cryptococce* or cryptococca* or TSS or ((endotoxi* or bacteriotoxi* or gram*) adj2 shock) or (blood* adj1 (infection* or poisoning*))).ab,hw,ti.	21,616
2	(norepinephrin* or ne or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or levarterenol or levonor or levonorepinephrine or levophed or levophed-bitartrate or neomelubrin or noradrec or noradrine or norexadrin or normetanephine or normetadrenaline or revarterenol or sympathin).ab,hw,ti.	11,141
3	(vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lyppressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentrad or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocturna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novodin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lyppressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylypressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllylvasopressin or triglycylvasopressin or variquel).ab,hw,ti.	4,503
4	((vasoactive or vasoconstrict* or vasopressor*) and (discontin* or taper* or wean* or order* or sequen* or strateg* or schedul*)).ab,hw,ti.	2,628
5	or/3-4	6,965
6	1 and 2 and 5	280
7	(pediatric* or child* or neonat* or newborn* or infan* or toddler* or girl* or boy* or adolesc* or teen* or youth or animal-stud* or animal-model*).ti.	159,274
8	(rat or rats or rodent* or mouse or mice or murine* or rabbit* or cat or cats or feline* or dog or dogs or canine* or porcine or swine or pig* or sheep or lamb* or ovine or equine* or horse* or primate* or veterinar*).ab,hw,ti.	35,004
9	(pediatric* or child* or neonat* or veterinar*).jw.	39,596
10	or/7-9	204,712
11	6 not 10	264
	Embase via Ovid (1974+):	Results from 5 Feb 2024
1	exp septic shock/ or exp sepsis/ or exp bloodstream infection/ or (sepsis or septic* or pyemi* or pyaemi* or pyohemi* or bacteremi* or bacteriemi* or bacteraemi* or bacillaemi* or bacillemi* or endotoxemi* or endotoxaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or cryptococce* or cryptococca* or TSS or ((endotoxi* or bacteriotoxi* or gram*) adj2 shock) or (blood* adj1 (infection* or poisoning*))).ab,kf,ti,dq.	506,703

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2	noradrenalin/ or (norepinephrin* or ne or noradrenalin* or adrenor or alginodia or arterenal or arterenal or baycain-green or levarterenol or levonor or levonorepinephrine or levophed or levophed-bitartrate or neomelubrin or noradrec or noradrine or norexadrin or normetanephine or normetadrenaline or revarterenol or sympathin).ab,kf,ti,dq,dy,tn.	229,598
3	vasopressin/ or exp vasopressin derivative/ or (vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdina or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylypressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysyvasopressin or triglycylvasopressin or variquel).ab,kf,ti,dq,dy,tn.	94,584
4	(vasoactive agent/ or vasoconstrictor agent/ or hypertensive agent/ or (vasoactive or vasoconstrict* or vasopressor*).ab,kf,ti,dq,dy,tn.) and (discontin* or taper* or wean* or order* or sequen* or strateg* or schedul*).ab,kf,ti,dq,hw.	21,608
5	or/3-4	114,660
6	1 and 2 and 5	2,864
7	exp juvenile/ not exp adult/	2,621,371
8	(exp animal/ or animal experiment/ or nonhuman/) not (exp human/ or human experiment/)	7,357,939
9	or/7-8	9,793,907
10	6 not 9	2,578
11	limit 10 to (english or portuguese or spanish)	2,486
	International Clinical Trials Registry Platform (ICTRP) from the World Health Organization (2005+) – *standard interface*	40
	(sepsis OR septic) AND (norepinephrine OR noradrenaline) AND (vasopressin OR vasopressins OR vasoactive OR vasoconstrictor OR vasoconstrictors OR vasopressor OR vasopressors)	
	MEDLINE via Ovid (1946+ and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily)	Results from 5 Feb 2024
1	exp Sepsis/ or (sepsis or septic* or pyemi* or pyaemi* or pyohemi* or bacteremi* or bacteriemi* or bacteriaemi* or bacillaemi* or bacillemi* or endotoxemi* or endotoxaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or cryptococcemi* or cryptococcaemi* or TSS or ((endotoxi* or bacteriotoxi* or gram*) adj2 shock) or (blood* adj1 (infection* or poisoning*))).ab,kf,ti.	293,882
2	exp Norepinephrine/ or (norepinephrin* or ne or noradrenalin* or adrenor or alginodia or arterenal or arterenal or baycain-green or levarterenol or levonor or levonorepinephrine or levophed or levophed-bitartrate or neomelubrin or noradrec or noradrine or norexadrin or normetanephine or normetadrenaline or revarterenol or sympathin).ab,kf,ti,nm.	157,564
3	exp Vasopressins/ or (vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdina or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylypressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysyvasopressin or triglycylvasopressin or variquel).ab,kf,ti,nm.	63,118
4	(vasoactive or vasoconstrict* or vasopressor*).ab,kf,ti,nm. and (discontin* or taper* or wean* or order* or sequen* or strateg* or schedul*).ab,kf,ti,hw.	12,841
5	or/3-4	75,197
6	1 and 2 and 5	641
7	(exp infant/ or exp child/ or adolescent/) not exp adult/	2,179,978
8	exp animals/ not humans/	5,193,699
9	or/7-8	7,373,214
10	6 not 9	540
11	limit 10 to (english or portuguese or spanish)	510

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	Scopus via Elsevier (1788+)	
	((TITLE-ABS-KEY(sepsis or septic* or pyemi* or pyaemi* or pyohemi* or bacteremi* or bacteriemi* or bacteriaemi* or bacillaemi* or bacillemi* or endotoxemi* or endotoxaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or cryptococce* or cryptococcaemi* or TSS) OR TITLE-ABS-KEY((endotoxi* or bacteriotoxi* or gram*) W/2 shock) OR TITLE-ABS-KEY(blood* W/1 (infection* or poisoning*)))) AND (TITLE-ABS-KEY(norepinephrin* or ne or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or levarterenol or levonor or levonorepinephrine or levophed or levophed-bitartrate or neomelubrin or noradrec or noradrine or norexadrin or normetanephine or normetadrenaline or reverterenol or sympathin)) AND ((TITLE-ABS-KEY(vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or coeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylypressin* or glypressin* or lucassin or remestyp or stemflovera or terlipresin* or terlivaz or triglycyllypressin or triglycyllysvasopressin or triglycylvasopressin or variquel) OR TITLE-ABS-KEY((vasoactive or vasoconstrict* or vasopressor*) AND (discontin* or taper* or wean* or order* or sequen* or strateg* or schedul*)))) AND NOT ((TITLE(pediatric* or child* or neonat* or newborn* or infan* or toddler* or girl* or boy* or adolesc* or teen* or youth or animal-stud* or animal-model*) OR TITLE-ABS-KEY(rat or rats or rodent* or mouse or mice or murine* or rabbit* or cat or cats or feline* or dog or dogs or canine* or porcine or swine or pig* or sheep or lamb* or ovine or equine* or horse* or primate* or veterinar*) OR SRCTITLE(pediatric* or child* or neonat* or veterinar*)))	74
	Web of Science Core Collection via Clarivate Analytics (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+):	658
8	#6 NOT #7 and English or Spanish or Portuguese (Languages)	
7	((TI=(p\$ediatric* or child* or neonat* or newborn* or infan* or toddler* or girl* or boy* or adolesc* or teen* or youth or animal-stud* or animal-model*)) OR TS=(rat or rats or rodent* or mouse or mice or murine* or rabbit* or cat or cats or feline* or dog or dogs or canine* or porcine or swine or pig* or sheep or lamb* or ovine or equine* or horse* or primate* or veterinar*)) OR SO=(p?ediatric* or child* or neonat* or veterinar*))	
6	#1 AND #2 AND #5	
5	#3 OR #4	
4	TS=((vasoactive or vasoconstrict* or vasopressor*) AND (discontin* or taper* or wean* or order* or sequen* or strateg* or schedul*))	
3	vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or coeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylypressin* or glypressin* or lucassin or remestyp or stemflovera or terlipresin* or terlivaz or triglycyllypressin or triglycyllysvasopressin or triglycylvasopressin or variquel (Topic)	
2	norepinephrin* or ne or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or levarterenol or levonor or levonorepinephrine or levophed or levophed-bitartrate or neomelubrin or noradrec or noradrine or norexadrin or normetanephine or normetadrenaline or reverterenol or sympathin (Topic)	
1	sepsis or septic* or pyemi* or pyaemi* or pyohemi* or bacteremi* or bacteriemi* or bacteriaemi* or bacillaemi* or bacillemi* or endotoxemi* or endotoxaemi* or fungemi* or fungaemi* or candidemi* or candidaemi* or cryptococce* or cryptococcaemi* or TSS (Topic) or (endotoxi* or bacteriotoxi* or gram*) NEAR/2 shock (Topic) or blood* NEAR/1 (infection* or poisoning*) (Topic)	

METHODOLOGICAL QUALITY

Table 2S - Cochrane risk of bias assessment for randomized clinical trials

Author	Outcome	Risk of bias from the randomization process	Risk of bias from intended intervention (assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall judgement
Jeon et al. ⁽⁵⁾	Hypotension (first hour)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mallmann et al. ⁽²²⁾	Hypotension (first 24 hours)	Some concerns	Some concerns	Low risk	Low risk	Low risk	Low risk

Table 3S - Newcastle-Ottawa Scale risk of bias for non-randomized studies

Author	Outcome	Domain of selection	Domain of comparability	Domain of outcome	Overall judgement
Song et al. ⁽⁴⁾	Hypotension (first 24 hours)	High risk	Unclear risk	High risk	High risk
Bauer et al. ⁽¹⁵⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Hammond et al. ⁽¹⁶⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Bissell et al. ⁽¹⁷⁾	Hypotension (first 24 hours)	High risk	High risk	High risk	High risk
Sacha et al. ⁽¹⁸⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Musallam et al. ⁽¹⁹⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Bredhold et al. ⁽²⁰⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Taylor et al. ⁽²¹⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk
Buckley et al. ⁽²³⁾	Hypotension (first 24 hours)	High risk	Low risk	High risk	High risk

FOREST AND FUNNEL PLOT OF SECONDARY OUTCOMES

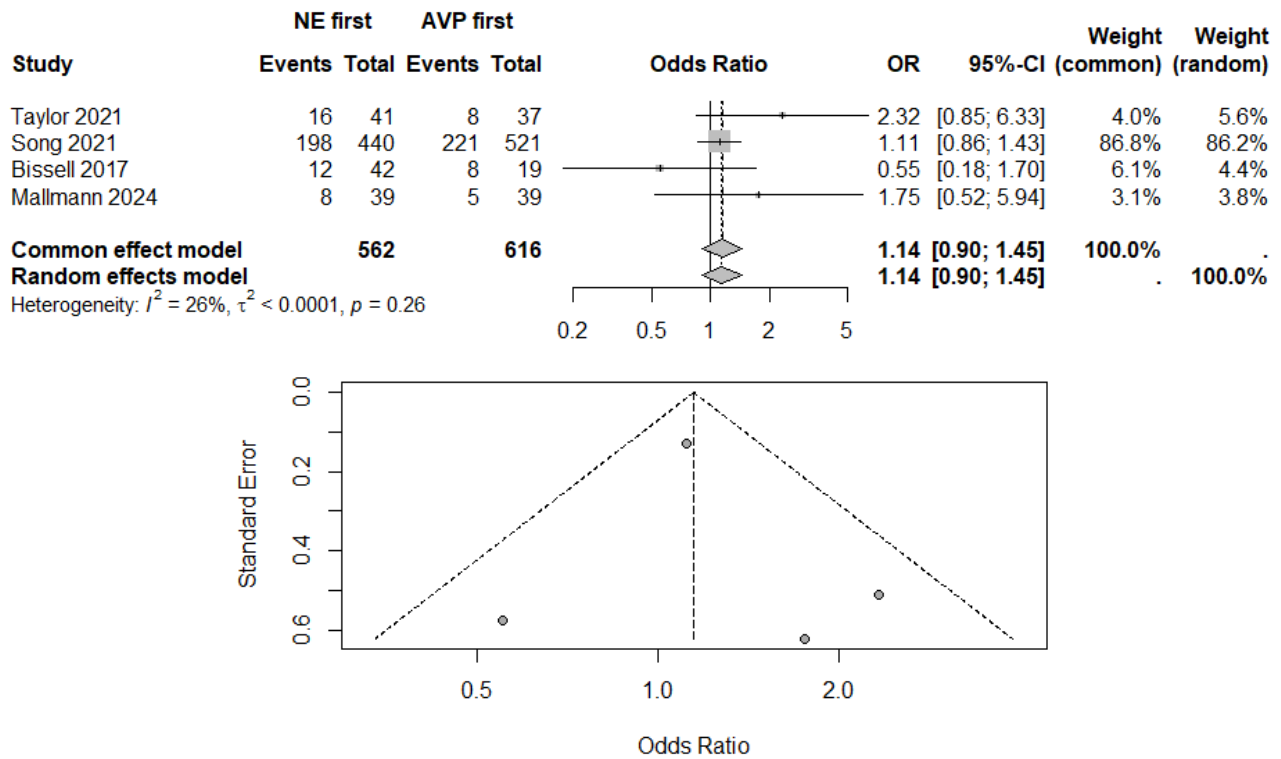


Figure 1S - Arrhythmia.

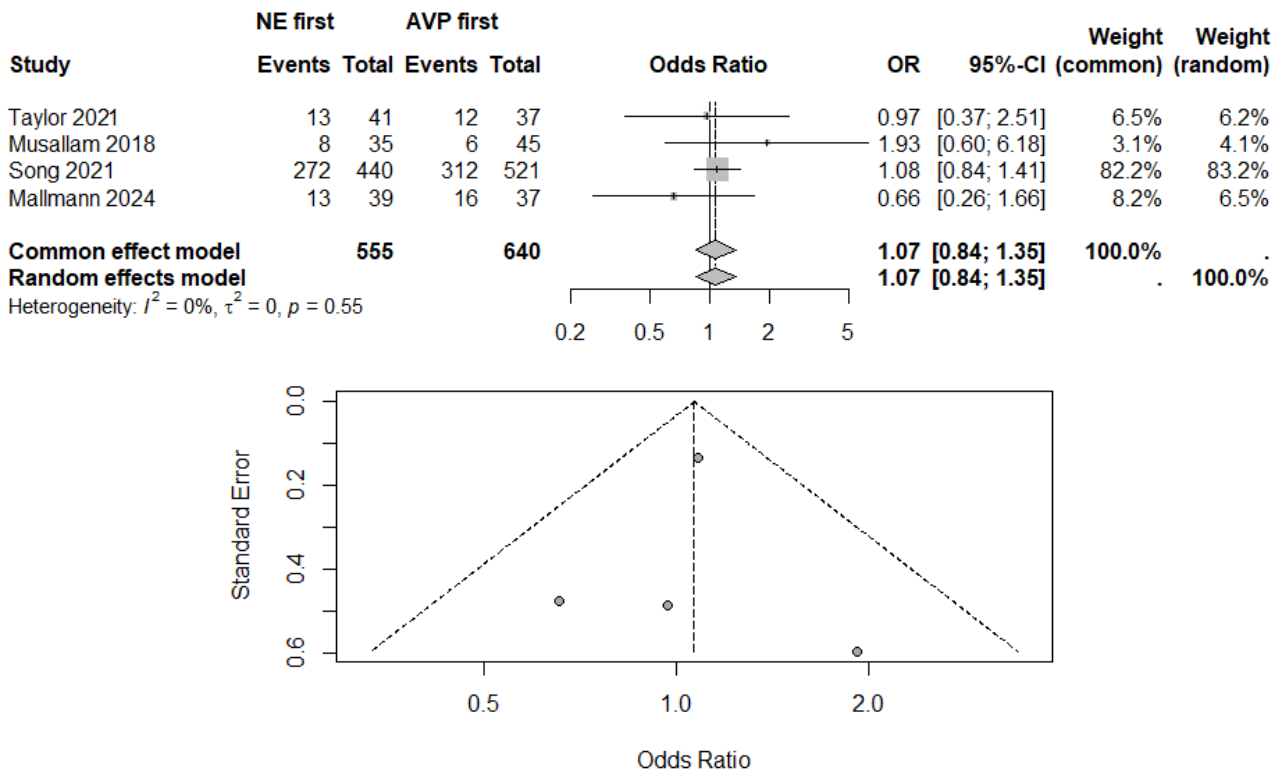


Figure 2S - Renal dysfunction.

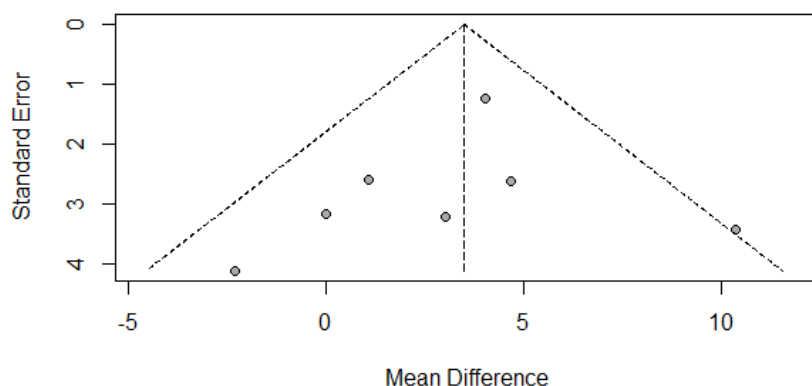
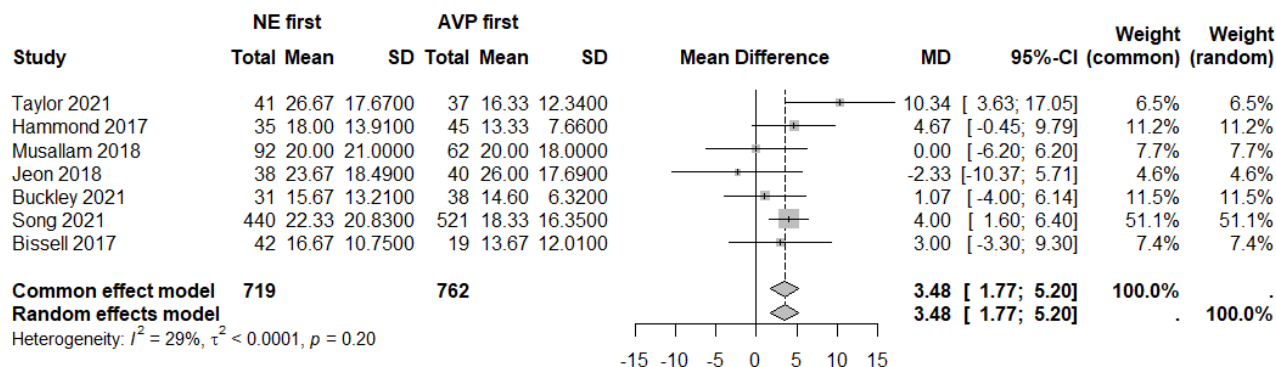


Figure 3S - Hospital length of stay.

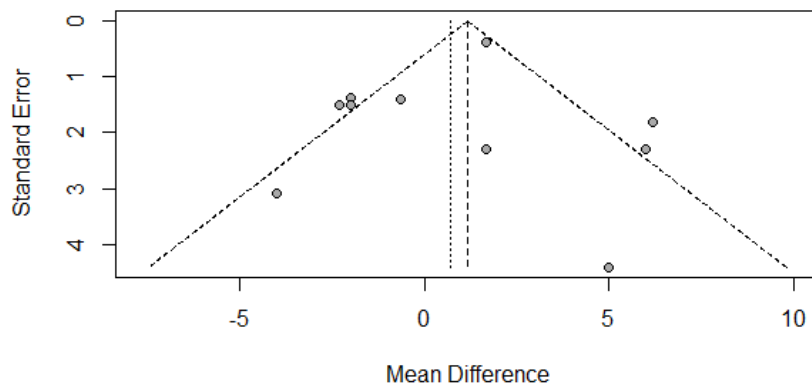
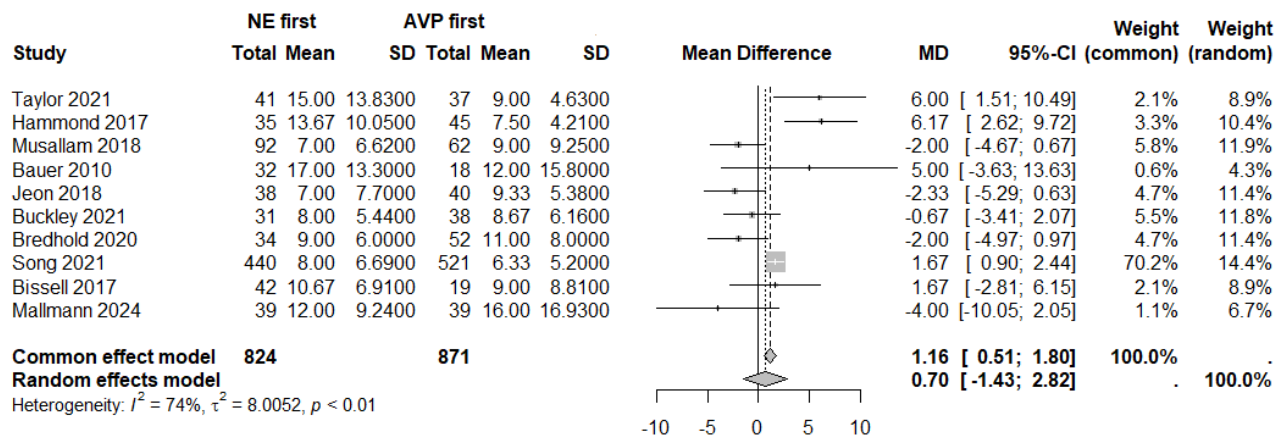


Figure 4S - Intensive care unit length of stay.

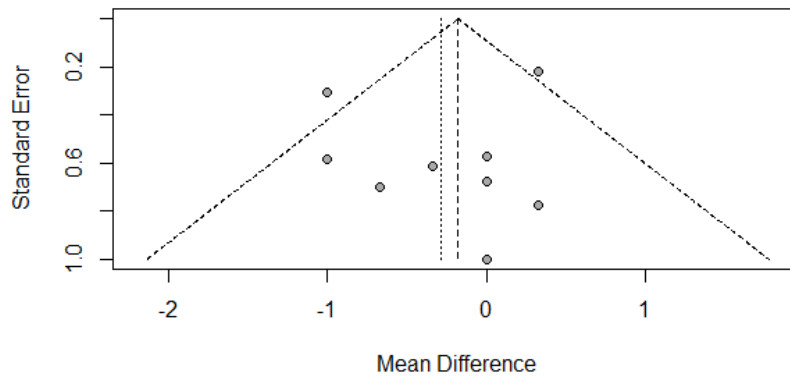
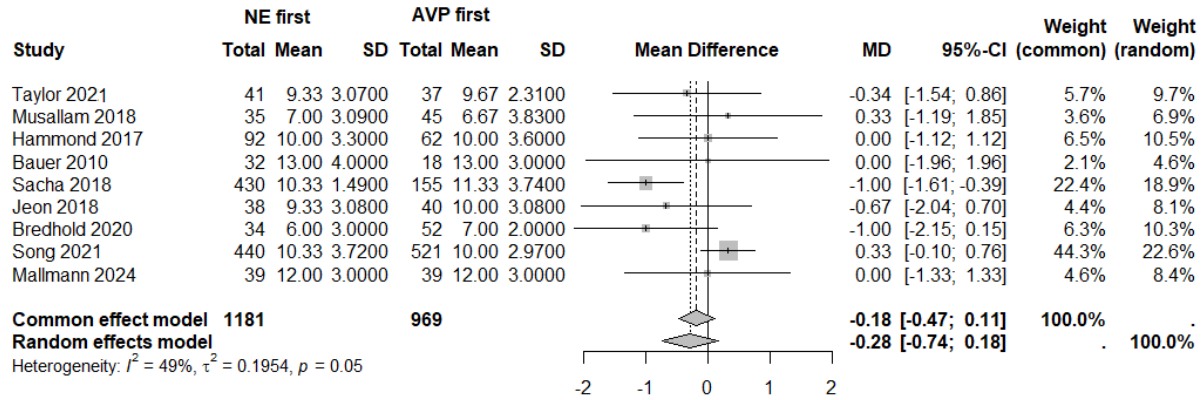


Figure 5S - SOFA 24 hours.

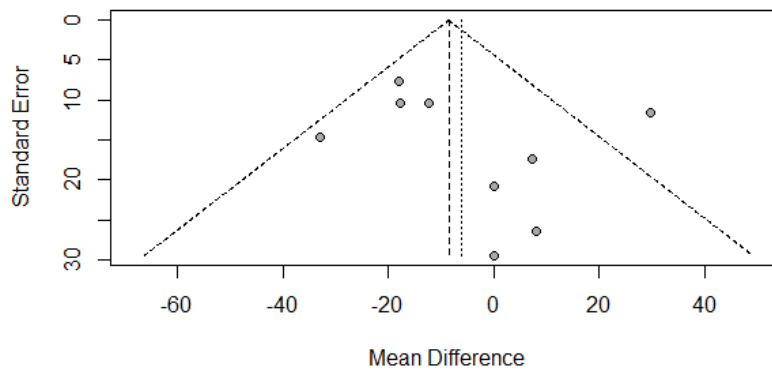
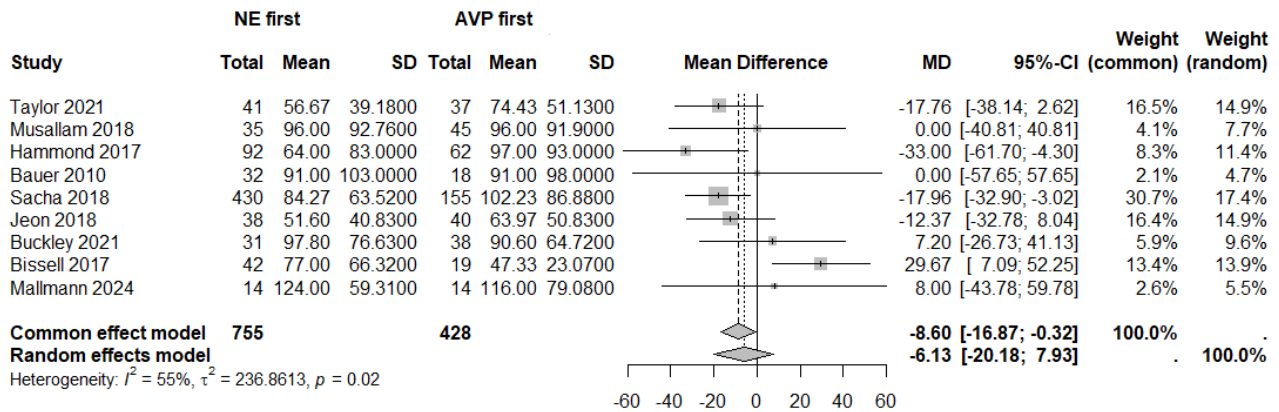


Figure 6S - Time on vasopressors.