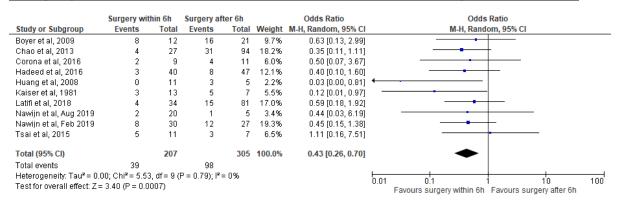
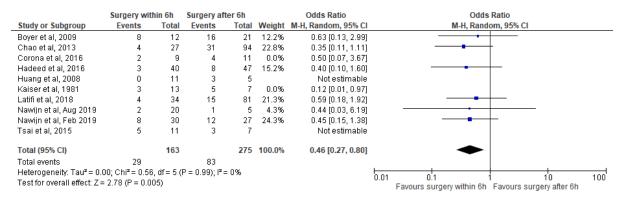
Additional file 4 Forrest plots for all (subgroup) analyses assessing surgical timing in relation to mortality and amputation due to necrotizing soft tissue infections

Surgery within 6 hours after presentation - mortality as outcome



Subgroup analysis: High-quality studies



Subgroup analysis: Studies published ≥2009

	Surgery wit	hin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Boyer et al, 2009	8	12	16	21	10.5%	0.63 [0.13, 2.99]	
Chao et al, 2013	4	27	31	94	19.7%	0.35 [0.11, 1.11]	
Corona et al, 2016	2	9	4	11	6.5%	0.50 [0.07, 3.67]	
Hadeed et al, 2016	3	40	8	47	13.1%	0.40 [0.10, 1.60]	
Huang et al, 2008	0	11	3	5	0.0%	0.03 [0.00, 0.81]	
Kaiser et al, 1981	3	13	5	7	0.0%	0.12 [0.01, 0.97]	
Latifi et al, 2018	4	34	15	81	18.4%	0.59 [0.18, 1.92]	
Nawijn et al, Aug 2019	2	20	1	5	3.7%	0.44 [0.03, 6.19]	
Nawijn et al, Feb 2019	8	30	12	27	21.0%	0.45 [0.15, 1.38]	
Tsai et al, 2015	5	11	3	7	7.1%	1.11 [0.16, 7.51]	
Total (95% CI)		183		293	100.0%	0.49 [0.30, 0.82]	◆
Total events	36		90				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 1.31	, df = 7 (l	P = 0.99); I ²	= 0%			
Test for overall effect: Z =	2.73 (P = 0.0	06)					0.01 0.1 1 10 100 Favours surgery within 6h Favours surgery after 6h
							Favours surgery within on Favours surgery after on

Subgroup analysis: Studies without limitation on affected body region by NSTI

	Surgery wit	hin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Boyer et al, 2009	8	12	16	21	0.0%	0.63 [0.13, 2.99]	
Chao et al, 2013	4	27	31	94	22.1%	0.35 [0.11, 1.11]	
Corona et al, 2016	2	9	4	11	0.0%	0.50 [0.07, 3.67]	
Hadeed et al, 2016	3	40	8	47	14.8%	0.40 [0.10, 1.60]	
Huang et al, 2008	0	11	3	5	0.0%	0.03 [0.00, 0.81]	
Kaiser et al, 1981	3	13	5	7	6.7%	0.12 [0.01, 0.97]	
Latifi et al, 2018	4	34	15	81	20.7%	0.59 [0.18, 1.92]	
Nawijn et al, Aug 2019	2	20	1	5	4.2%	0.44 [0.03, 6.19]	
Nawijn et al, Feb 2019	8	30	12	27	23.6%	0.45 [0.15, 1.38]	
Tsai et al, 2015	5	11	3	7	8.0%	1.11 [0.16, 7.51]	
Total (95% CI)		175		268	100.0%	0.44 [0.25, 0.75]	•
Total events	29		75				
Heterogeneity: Tau ² = 0.1		3 df = 6 (= 0%			
Test for overall effect: Z =			0.01/11				0.01 0.1 1 10 100
- correction of orall effect. Z -		007					Favours surgery within 6h Favours surgery after 6h

	Surgery wit	hin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Boyer et al, 2009	8	12	16	21	13.3%	0.63 [0.13, 2.99]	
Chao et al, 2013	4	27	31	94	0.0%	0.35 [0.11, 1.11]	
Corona et al, 2016	2	9	4	11	8.2%	0.50 [0.07, 3.67]	
Hadeed et al, 2016	3	40	8	47	16.6%	0.40 [0.10, 1.60]	
Huang et al, 2008	0	11	3	5	0.0%	0.03 [0.00, 0.81]	
Kaiser et al, 1981	3	13	5	7	7.5%	0.12 [0.01, 0.97]	
Latifi et al, 2018	4	34	15	81	23.2%	0.59 [0.18, 1.92]	
Nawijn et al, Aug 2019	2	20	1	5	4.7%	0.44 [0.03, 6.19]	
Nawijn et al, Feb 2019	8	30	12	27	26.5%	0.45 [0.15, 1.38]	
Tsai et al, 2015	5	11	3	7	0.0%	1.11 [0.16, 7.51]	
Total (95% CI)		158		199	100.0%	0.45 [0.25, 0.79]	•
Total events	30		61				
Heterogeneity: Tau ² = 0.	00; Chi ² = 1.95	5, df = 6 (P = 0.92); I ²	= 0%			
Test for overall effect: Z =	•						0.01 0.1 1 10 100
		,					Favours surgery within 6h Favours surgery after 6h

Surgery within 6 hours after presentation - amputation as outcome

	Surgery wit	hin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Corona et al, 2016	1	9	3	11	8.4%	0.33 [0.03, 3.93]	
Hadeed et al, 2016	6	29	13	31	38.6%	0.36 [0.11, 1.14]	
Huang et al, 2008	4	11	0	5	5.2%	6.60 [0.29, 149.77]	
Kaiser et al, 1981	0	7	1	3	4.1%	0.11 [0.00, 3.70]	· · · · · · · · · · · · · · · · · · ·
Mittapalli et al, 2015	2	6	3	18	11.5%	2.50 [0.31, 20.45]	
Nawijn et al, Aug 2019	1	14	0	4	4.5%	1.00 [0.03, 29.19]	
Nawijn et al, Feb 2019	4	16	3	15	17.6%	1.33 [0.24, 7.28]	
Tsai et al, 2015	2	11	2	7	10.1%	0.56 [0.06, 5.24]	
Total (95% CI)		103		94	100.0%	0.68 [0.34, 1.39]	-
Total events	20		25				
Heterogeneity: Tau ² = 0.	00; Chi ² = 6.72	2, df = 7 (P = 0.46); I ² :	= 0%			
Test for overall effect: Z =	= 1.05 (P = 0.3	0)					0.01 0.1 1 10 100 Favours surgery within 6h Favours surgery after 6h

Subgroup analysis: High-quality studies

	Surgery wit	thin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Corona et al, 2016	1	9	3	11	0.0%	0.33 [0.03, 3.93]	
Hadeed et al, 2016	6	29	13	31	63.6%	0.36 [0.11, 1.14]	
Huang et al, 2008	4	11	0	5		Not estimable	
Kaiser et al, 1981	0	7	1	3	0.0%	0.11 [0.00, 3.70]	
Mittapalli et al, 2015	2	6	3	18	0.0%	2.50 [0.31, 20.45]	
Nawijn et al, Aug 2019	1	14	0	4	7.4%	1.00 [0.03, 29.19]	
Nawijn et al, Feb 2019	4	16	3	15	29.1%	1.33 [0.24, 7.28]	
Tsai et al, 2015	2	11	2	7		Not estimable	
Total (95% CI)		59		50	100.0%	0.57 [0.23, 1.42]	
Total events	11		16				
Heterogeneity: Tau ² = 0.	00; Chi ² = 1.68	3, df = 2 (P = 0.43); I ² =	= 0%			
Test for overall effect: Z							0.01 0.1 1 10 100 Favours surgery within 6h Favours surgery after 6h

Subgroup analysis: Studies published ≥2009

	Surgery wit	hin 6h	Surgery aff	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Corona et al, 2016	1	9	3	11	9.2%	0.33 [0.03, 3.93]	
Hadeed et al, 2016	6	29	13	31	42.6%	0.36 [0.11, 1.14]	
Huang et al, 2008	4	11	0	5	0.0%	6.60 [0.29, 149.77]	
Kaiser et al, 1981	0	7	1	3	0.0%	0.11 [0.00, 3.70]	
Mittapalli et al, 2015	2	6	3	18	12.7%	2.50 [0.31, 20.45]	
Nawijn et al, Aug 2019	1	14	0	4	4.9%	1.00 [0.03, 29.19]	
Nawijn et al, Feb 2019	4	16	3	15	19.5%	1.33 [0.24, 7.28]	
Tsai et al, 2015	2	11	2	7	11.1%	0.56 [0.06, 5.24]	
Total (95% CI)		85		86	100.0%	0.65 [0.31, 1.38]	-
Total events	16		24				
Heterogeneity: Tau ² = 0.1	00; Chi ² = 3.64	, df = 5 (P = 0.60); I ² =	= 0%			
Test for overall effect: Z =	= 1.12 (P = 0.2	6)					0.01 0.1 1 10 100 Favours surgery within 6h Favours surgery after 6h

Subgroup analysis: Studies without limitation on affected body region by NSTI

Huang et al, 2008 4 11 0 5 0.0% 6.60 [0.29, 149.77] Kaiser et al, 1981 0 7 1 3 4.8% 0.11 [0.00, 3.70] Mittapalli et al, 2015 2 6 3 18 13.3% 2.50 [0.31, 20.45] Nawijn et al, Aug 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total events 15 22 22 15 22 Heterogeneity: Tau ² = 0.00: Chi ² = 4.33; df = 5 (P = 0.50): P = 0% 0% 0.64 [0.30, 1.38]		n Odds Ratio Odds Ratio	Sur	
Hadeed et al, 2016 6 29 13 31 44.7% 0.36 [0.11, 1.14] Huang et al, 2008 4 11 0 5 0.0% 6.60 [0.29, 149.77] Kaiser et al, 1981 0 7 1 3 4.8% 0.11 [0.00, 3.70] Wittapalli et al, 2015 2 6 3 18 13.3% 2.50 [0.31, 20.45] Nawijn et al, Feb 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Total (95% Cl) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 22 15 22 Heterogenetic Tau ² = 0.00°, Ch ² = 4 33. off = 5 (P = 0.50°, P = 0.5%) 15 16 16	tudy or Subgroup	tal Weight M-H, Random, 95% Cl M-H, Random, 95% Cl	I Ev	
Huang et al, 2008 4 11 0 5 0.0% 6.60 [0.29, 149.77] Kaiser et al, 1981 0 7 1 3 4.8% 0.11 [0.00, 3.70] Mittapalli et al, 2015 2 6 3 18 13.3% 2.50 [0.31, 20.45] Nawijn et al, Aug 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total events 15 22 22 15 22 Heterogeneity: Tau ² = 0.00: Ch ² = 4.33; df = 5 (P = 0.50); P = 0% 0% 0.64 [0.30, 1.38]	orona et al, 2016	11 0.0% 0.33 [0.03, 3.93])	
Kaiser et al, 1981 0 7 1 3 4.8% 0.11 [0.00, 3.70] Mittapalli et al, 2015 2 6 3 18 13.3% 2.50 [0.31, 20.45] Nawijn et al, Aug 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total (95% CI) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 Heterogenetik: Tauž= 0.00: Chiz = 4 33 df = 5 (P = 0.50): (P = 0%	ladeed et al, 2016	31 44.7% 0.36 [0.11, 1.14])	
Mittapalli et al, 2015 2 6 3 18 13.3% 2.50 [0.31, 20.45] Nawijn et al, Aug 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total (95% Cl) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 22 Heterogenepits Tauj= -0.00; Chiz= -0.30; If = 5 (P = 0.50); IE = 0.0% 14 14 14	luang et al, 2008	5 0.0% 6.60 [0.29, 149.77]		
Nawijn et al, Aug 2019 1 14 0 4 5.2% 1.00 [0.03, 29.19] Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total (95% CI) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 Heterogenetic Tau2 = 0.00: Chi² = 4.33 df = 5 (P = 0.50); P = 0.0%	aiser et al, 1981	3 4.8% 0.11 [0.00, 3.70]	,	
Nawijn et al, Feb 2019 4 16 3 15 20.4% 1.33 [0.24, 7.28] Tsai et al, 2015 2 11 2 7 11.7% 0.56 [0.06, 5.24] Total (95% CI) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 Heterogeneity: Tau ² = 0.00: Chi ² = 4.33 df = 5 (P = 0.50): I ² = 0%	littapalli et al, 2015	18 13.3% 2.50 [0.31, 20.45])	
Tsai et al, 2015 2 11 2 7 11.7% 0.58 [0.06, 5.24] Total (95% Cl) 83 78 100.0% 0.64 [0.30, 1.38] Total events 15 22 Heterogenetity Tau2 = 0.00: Cbi2 = 4.33 df = 5 (P = 0.50): P = 0%	lawijn et al, Aug 2019	4 5.2% 1.00 [0.03, 29.19]	Ļ	-
Total (95% CI) 83 78 100.0% 0.64 [0.30, 1.38]	lawijn et al, Feb 2019	15 20.4% 1.33 [0.24, 7.28]	6	
Total events 15 22 Heterographic Tau? = 0.00: Chi? = 4.33 df = 5 (P = 0.50): P = 0%	sai et al, 2015	7 11.7% 0.56 [0.06, 5.24]		
Heterogeneity: Tau2 = 0.00; Cbi2 = 4.33, df = 5 (P = 0.50); I2 = 0%	otal (95% CI)	78 100.0% 0.64 [0.30, 1.38]	3	
Heterogeneity: Tau ² = 0.00; Chi ² = 4.33, df = 5 (P = 0.50); I ² = 0%	otal events			
	leterogeneity: Tau² = 0.		(P = 0)	
		0.01 0.1 1 10 Favours surgerv within 6h Favours surgerv after 6	· -	10

	Surgery wit	hin 6h	Surgery af	ter 6h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Corona et al, 2016	1	9	3	11	9.9%	0.33 [0.03, 3.93]	
Hadeed et al, 2016	6	29	13	31	45.6%	0.36 [0.11, 1.14]	
Huang et al, 2008	4	11	0	5	0.0%	6.60 [0.29, 149.77]	
Kaiser et al, 1981	0	7	1	3	4.9%	0.11 [0.00, 3.70]	· · · · · · · · · · · · · · · · · · ·
Mittapalli et al, 2015	2	6	3	18	13.6%	2.50 [0.31, 20.45]	
Nawijn et al, Aug 2019	1	14	0	4	5.3%	1.00 [0.03, 29.19]	
Nawijn et al, Feb 2019	4	16	3	15	20.8%	1.33 [0.24, 7.28]	
Tsai et al, 2015	2	11	2	7	0.0%	0.56 [0.06, 5.24]	
Total (95% CI)		81		82	100.0%	0.61 [0.28, 1.32]	
Total events	14		23				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 4.57	, df = 5 (P = 0.47); I ² :	= 0%			
Test for overall effect: Z =							0.01 0.1 1 10 100 Favours surgery within 6h Favours surgery after 6h
							avours surgery within on Favours surgery alter on

Surgery within 12 hours after presentation - mortality as outcome

	Surgery with	in 12h	Surgery after	er 12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balci et al, 2009	0	6	2	5	1.6%	0.11 [0.00, 2.93]	· · · · · · · · · · · · · · · · · · ·
Boyer et al, 2009	9	16	15	17	5.4%	0.17 [0.03, 1.01]	
Chao et al, 2013	8	53	27	68	21.3%	0.27 [0.11, 0.66]	
Corona et al, 2016	3	14	3	6	4.1%	0.27 [0.04, 2.11]	
Huang et al, 2008	2	13	1	3	2.1%	0.36 [0.02, 6.19]	
Kaiser et al, 1981	4	15	4	5	2.8%	0.09 [0.01, 1.08]	·
Kobayashi et al, 2011	1	22	7	25	3.6%	0.12 [0.01, 1.09]	
Lee et al, 2014	10	67	8	33	15.7%	0.55 [0.19, 1.55]	
Lille et al, 1996	1	17	3	12	3.0%	0.19 [0.02, 2.08]	
Nawijn et al, Aug 2019	3	24	0	2	1.6%	0.81 [0.03, 20.78]	
Nawijn et al, Feb 2019	12	42	9	28	15.9%	0.84 [0.30, 2.38]	
Pakula et al, 2012	5	35	3	19	7.1%	0.89 [0.19, 4.21]	
Sudarsky et al, 1987	0	7	2	26	1.7%	0.65 [0.03, 15.16]	
Tsai et al, 2010	12	54	6	17	12.2%	0.52 [0.16, 1.71]	
Tsai et al, 2015	7	16	1	2	2.0%	0.78 [0.04, 14.75]	
Total (95% CI)		401		268	100.0%	0.41 [0.27, 0.61]	◆
Total events	77		91				
Heterogeneity: Tau ² = 0.	.00; Chi ² = 9.31,	df = 14 (P = 0.81); I ² =	0%			
Test for overall effect: Z:	= 4.27 (P < 0.00	01)					0.01 0.1 i 10 100 Favours surgery within 12h Favours surgery after 12h

Subgroup analysis: High-quality studies



Subgroup analysis: Studies published ≥2009

	Surgery with	in 12h	Surgery after	er 12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balci et al, 2009	0	6	2	5	1.7%	0.11 [0.00, 2.93]	· • · · · · · · · · · · · · · · · · · ·
Boyer et al, 2009	9	16	15	17	6.0%	0.17 [0.03, 1.01]	
Chao et al, 2013	8	53	27	68	23.6%	0.27 [0.11, 0.66]	_
Corona et al, 2016	3	14	3	6	4.5%	0.27 [0.04, 2.11]	· · · · · · · · · · · · · · · · · · ·
Huang et al, 2008	2	13	1	3	0.0%	0.36 [0.02, 6.19]	
Kaiser et al, 1981	4	15	4	5	0.0%	0.09 [0.01, 1.08]	
Kobayashi et al, 2011	1	22	7	25	3.9%	0.12 [0.01, 1.09]	·
Lee et al, 2014	10	67	8	33	17.4%	0.55 [0.19, 1.55]	_
Lille et al, 1996	1	17	3	12	0.0%	0.19 [0.02, 2.08]	
Nawijn et al, Aug 2019	3	24	0	2	1.8%	0.81 [0.03, 20.78]	
Nawijn et al, Feb 2019	12	42	9	28	17.5%	0.84 [0.30, 2.38]	
Pakula et al, 2012	5	35	3	19	7.8%	0.89 [0.19, 4.21]	
Sudarsky et al, 1987	0	7	2	26	0.0%	0.65 [0.03, 15.16]	
Tsai et al, 2010	12	54	6	17	13.5%	0.52 [0.16, 1.71]	
Tsai et al, 2015	7	16	1	2	2.2%	0.78 [0.04, 14.75]	· · · · · · · · · · · · · · · · · · ·
Total (95% CI)		349		222	100.0%	0.43 [0.28, 0.67]	◆
Total events	70		81				
Heterogeneity: Tau ² = 0.0	00; Chi² = 7.32,	df = 10 (l	P = 0.69); I ² =	0%			0.01 0.1 1 10 100
Test for overall effect: Z =	3.76 (P = 0.00	02)					Favours surgery within 12h Favours surgery after 12h

Subgroup analysis: Studies without limitation on affected body region by NSTI

	Surgery within	n 12h	Surgery afte	r 12 h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Balci et al, 2009	0	6	2	5	0.0%	0.11 [0.00, 2.93]	
Boyer et al, 2009	9	16	15	17	0.0%	0.17 [0.03, 1.01]	
Chao et al, 2013	8	53	27	68	24.5%	0.27 [0.11, 0.66]	
Corona et al, 2016	3	14	3	6	0.0%	0.27 [0.04, 2.11]	
Huang et al, 2008	2	13	1	3	0.0%	0.36 [0.02, 6.19]	
Kaiser et al, 1981	4	15	4	5	3.2%	0.09 [0.01, 1.08]	• • •
Kobayashi et al, 2011	1	22	7	25	4.1%	0.12 [0.01, 1.09]	
Lee et al, 2014	10	67	8	33	18.1%	0.55 [0.19, 1.55]	
Lille et al, 1996	1	17	3	12	3.4%	0.19 [0.02, 2.08]	
Nawijn et al, Aug 2019	3	24	0	2	1.9%	0.81 [0.03, 20.78]	
Nawijn et al, Feb 2019	12	42	9	28	18.3%	0.84 [0.30, 2.38]	
Pakula et al, 2012	5	35	3	19	8.1%	0.89 [0.19, 4.21]	
Sudarsky et al, 1987	0	7	2	26	2.0%	0.65 [0.03, 15.16]	· · · · · · · · · · · · · · · · · · ·
Tsai et al, 2010	12	54	6	17	14.0%	0.52 [0.16, 1.71]	
Tsai et al, 2015	7	16	1	2	2.3%	0.78 [0.04, 14.75]	
Total (95% CI)		352		237	100.0%	0.45 [0.29, 0.70]	◆
Total events	63		70				
Heterogeneity: Tau ² = 0.	00; Chi² = 7.44, d	df = 10 (l	^o = 0.68); I ^z = 0	1%			
Test for overall effect: Z =	= 3.54 (P = 0.000	14)					0.01 0.1 1 1 10 100 Favours surgery within 12h Favours surgery after 12h

	Surgery with	in 12h	Surgery afte	r 12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Balci et al, 2009	0	6	2	5	3.4%	0.11 [0.00, 2.93]	← → − − −
Boyer et al, 2009	9	16	15	17	11.6%	0.17 [0.03, 1.01]	
Chao et al, 2013	8	53	27	68	0.0%	0.27 [0.11, 0.66]	
Corona et al, 2016	3	14	3	6	8.7%	0.27 [0.04, 2.11]	
Huang et al, 2008	2	13	1	3	0.0%	0.36 [0.02, 6.19]	
Kaiser et al, 1981	4	15	4	5	6.0%	0.09 [0.01, 1.08]	· · · · · · · · · · · · · · · · · · ·
Kobayashi et al, 2011	1	22	7	25	7.6%	0.12 [0.01, 1.09]	
Lee et al, 2014	10	67	8	33	0.0%	0.55 [0.19, 1.55]	
Lille et al, 1996	1	17	3	12	6.3%	0.19 [0.02, 2.08]	
Nawijn et al, Aug 2019	3	24	0	2	3.5%	0.81 [0.03, 20.78]	
Nawijn et al, Feb 2019	12	42	9	28	34.0%	0.84 [0.30, 2.38]	
Pakula et al, 2012	5	35	3	19	15.1%	0.89 [0.19, 4.21]	
Sudarsky et al, 1987	0	7	2	26	3.7%	0.65 [0.03, 15.16]	
Tsai et al, 2010	12	54	6	17	0.0%	0.52 [0.16, 1.71]	
Tsai et al, 2015	7	16	1	2	0.0%	0.78 [0.04, 14.75]	
Total (95% CI)		198		145	100.0%	0.41 [0.22, 0.74]	◆
Total events	38		48				
Heterogeneity: Tau ² = 0.	00; Chi ² = 7.83,	df = 9 (P	= 0.55); I ² = 09	%			
Test for overall effect: Z :	= 2.92 (P = 0.00	3)					0.01 0.1 1 10 100 Favours surgery within 12h Favours surgery after 12h

Surgery within 12 hours after presentation - amputation as outcome

	Surgery with	in 12h	Surgery afte	r 12h		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Corona et al, 2016	2	14	2	6	17.3%	0.33 [0.03, 3.20]		
Huang et al, 2008	4	13	0	3	8.8%	3.32 [0.14, 78.81]		_
Kaiser et al, 1981	0	7	1	3	7.2%	0.11 [0.00, 3.70]	• • •	
Mittapalli et al, 2015	2	8	3	16	21.4%	1.44 [0.19, 11.04]		
Nawijn et al, Aug 2019	1	17	0	1	6.8%	0.27 [0.01, 10.09]	• • •	
Nawijn et al, Feb 2019	4	21	3	11	30.0%	0.63 [0.11, 3.49]		
Tsai et al, 2015	4	16	0	2	8.5%	1.80 [0.07, 45.14]		
Total (95% CI)		96		42	100.0%	0.71 [0.28, 1.82]		
Total events	17		9					
Heterogeneity: Tau ² = 0.1	00; Chi ² = 3.51,	df = 6 (P	= 0.74); l ² = 09	%				
Test for overall effect: Z =	= 0.71 (P = 0.48)					0.01 0.1 1 10 Favours surgery within 12h Favours surgery after 12h	100

Subgroup analysis: High-quality studies

	Surgery with	in 12h	Surgery after	12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Corona et al, 2016	2	14	2	6	0.0%	0.33 [0.03, 3.20]	
Huang et al, 2008	4	13	0	3		Not estimable	
Kaiser et al, 1981	0	7	1	3	0.0%	0.11 [0.00, 3.70]	
Mittapalli et al, 2015	2	8	3	16	0.0%	1.44 [0.19, 11.04]	
Nawijn et al, Aug 2019	1	17	0	1	18.4%	0.27 [0.01, 10.09]	•
Nawijn et al, Feb 2019	4	21	3	11	81.6%	0.63 [0.11, 3.49]	
Tsai et al, 2015	4	16	0	2		Not estimable	
Total (95% CI)		38		12	100.0%	0.54 [0.11, 2.54]	
Total events	5		3				
Heterogeneity: Tau ² = 0.1	00; Chi ² = 0.17,	df = 1 (P	= 0.68); I ² = 09	6			
Test for overall effect: Z =	= 0.78 (P = 0.43))					0.01 0.1 1 10 100 Favours surgery within 12h Favours surgery after 12h

Subgroup analysis: Studies published ≥2009

	Surgery with	in 12h	Surgery afte	r 12h		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% Cl	
Corona et al, 2016	2	14	2	6	20.6%	0.33 [0.03, 3.20]			
Huang et al, 2008	4	13	0	3	0.0%	3.32 [0.14, 78.81]			
Kaiser et al, 1981	0	7	1	3	0.0%	0.11 [0.00, 3.70]			
Mittapalli et al, 2015	2	8	3	16	25.5%	1.44 [0.19, 11.04]			
Nawijn et al, Aug 2019	1	17	0	1	8.1%	0.27 [0.01, 10.09]	•		
Nawijn et al, Feb 2019	4	21	3	11	35.7%	0.63 [0.11, 3.49]			
Tsai et al, 2015	4	16	0	2	10.1%	1.80 [0.07, 45.14]			-
Total (95% CI)		76		36	100.0%	0.71 [0.25, 1.98]			
Total events	13		8						
Heterogeneity: Tau ² = 0.	00; Chi² = 1.51,	df = 4 (P	= 0.82); I ^z = 0 ^o	%			L		400
Test for overall effect: Z	= 0.66 (P = 0.51)					0.01	0.1 1 10 Favours surgery within12h Favours surgery after 12h	100

Subgroup analysis: Studies without limitation on affected body region by NSTI

	Surgery with	in 12h	Surgery after	r 12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Corona et al, 2016	2	14	2	6	0.0%	0.33 [0.03, 3.20]	
Huang et al, 2008	4	13	0	3	0.0%	3.32 [0.14, 78.81]	
Kaiser et al, 1981	0	7	1	3	9.7%	0.11 [0.00, 3.70]	←
Mittapalli et al, 2015	2	8	3	16	28.9%	1.44 [0.19, 11.04]	
Nawijn et al, Aug 2019	1	17	0	1	9.2%	0.27 [0.01, 10.09]	• • •
Nawijn et al, Feb 2019	4	21	3	11	40.6%	0.63 [0.11, 3.49]	
Tsai et al, 2015	4	16	0	2	11.5%	1.80 [0.07, 45.14]	
Total (95% CI)		69		33	100.0%	0.71 [0.24, 2.11]	
Total events	11		7				
Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =			= 0.71); I ^z = 09	6			0.01 0.1 10 10 Favours surgery within 12h Favours surgery after 12h

	Surgery withi	n 12h	Surgery after	12h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Corona et al, 2016	2	14	2	6	20.9%	0.33 [0.03, 3.20]	
Huang et al, 2008	4	13	0	3	0.0%	3.32 [0.14, 78.81]	
Kaiser et al, 1981	0	7	1	3	8.7%	0.11 [0.00, 3.70]	· · · · · · · · · · · · · · · · · · ·
Mittapalli et al, 2015	2	8	3	16	25.9%	1.44 [0.19, 11.04]	
Nawijn et al, Aug 2019	1	17	0	1	8.2%	0.27 [0.01, 10.09]	· · · · · ·
Nawijn et al, Feb 2019	4	21	3	11	36.3%	0.63 [0.11, 3.49]	
Tsai et al, 2015	4	16	0	2	0.0%	1.80 [0.07, 45.14]	
Total (95% CI)		67		37	100.0%	0.55 [0.19, 1.54]	
Total events	9		9				
Heterogeneity: Tau ² = 0.1	00; Chi² = 2.02, (df = 4 (P	= 0.73); I ² = 0%	6			
Test for overall effect: Z =	= 1.14 (P = 0.25)						0.01 0.1 1 10 100 Favours surgery within 12h Favours surgery after 12h

Surgery within 24 hours after presentation - mortality as outcome

	Surgery with	in 24h	Surgery aft	er 24h		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Bair et al, 2009	8	38	10	68	10.3%	1.55 [0.55, 4.33]		
Balci et al, 2009	1	8	1	3	1.6%	0.29 [0.01, 6.91]		
Boyer et al, 2009	23	32	1	1	1.5%	0.82 [0.03, 22.09]		
Chao et al, 2013	20	90	15	31	12.7%	0.30 [0.13, 0.72]		
Corona et al, 2016	6	18	0	2	1.6%	2.60 [0.11, 62.57]		
George et al, 2009	8	61	0	11	1.9%	3.65 [0.20, 67.92]		
Huang et al, 2008	2	14	1	2	1.6%	0.17 [0.01, 3.89]	←	
Huang et al, 2011	38	280	19	192	18.1%	1.43 [0.80, 2.56]		+
Kaiser et al, 1981	6	17	2	3	2.3%	0.27 [0.02, 3.67]		
Kalaivani et al, 2012	10	35	5	25	8.2%	1.60 [0.47, 5.44]		
Lee et al, 2014	12	81	6	19	9.0%	0.38 [0.12, 1.18]		
Nawijn et al, Feb 2019	14	51	7	20	9.4%	0.70 [0.23, 2.12]		
Ogilvie et al, 2006	13	134	1	16	3.4%	1.61 [0.20, 13.21]		
Palmer et al, 1995	10	21	3	9	5.3%	1.82 [0.36, 9.27]		
Park et al, 2016	4	20	3	10	4.7%	0.58 [0.10, 3.33]		
Stephenson et al, 1992	2	7	12	22	4.3%	0.33 [0.05, 2.10]		
Wang et al, 1992	3	14	3	4	2.3%	0.09 [0.01, 1.22]	•	
Yu et al, 2004	2	10	0	3	1.5%	2.06 [0.08, 54.80]		
Total (95% CI)		931		441	100.0%	0.79 [0.52, 1.20]		•
Total events	182		89					
Heterogeneity: Tau ² = 0.1	6; Chi ² = 22.03,	df = 17 (P = 0.18); P =	23%				0.1 1 10 100
Test for overall effect: Z =							0.01	0.1 1 10 100 Favours surgery within24h Favours surgery after 24h

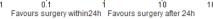
Subgroup analysis: High-quality studies

	Surgery with	in 24h	Surgery aft	er 24h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bair et al, 2009	8	38	10	68	0.0%	1.55 [0.55, 4.33]	
Balci et al, 2009	1	8	1	3	0.0%	0.29 [0.01, 6.91]	
Boyer et al, 2009	23	32	1	1	4.7%	0.82 [0.03, 22.09]	
Chao et al, 2013	20	90	15	31	24.8%	0.30 [0.13, 0.72]	
Corona et al, 2016	6	18	0	2	0.0%	2.60 [0.11, 62.57]	
George et al, 2009	8	61	0	11	0.0%	3.65 [0.20, 67.92]	
Huang et al, 2008	2	14	1	2	0.0%	0.17 [0.01, 3.89]	
Huang et al, 2011	38	280	19	192	30.0%	1.43 [0.80, 2.56]	
Kaiser et al, 1981	6	17	2	3	0.0%	0.27 [0.02, 3.67]	
Kalaivani et al, 2012	10	35	5	25	0.0%	1.60 [0.47, 5.44]	
Lee et al, 2014	12	81	6	19	19.9%	0.38 [0.12, 1.18]	
Nawijn et al, Feb 2019	14	51	7	20	20.6%	0.70 [0.23, 2.12]	
Ogilvie et al, 2006	13	134	1	16	0.0%	1.61 [0.20, 13.21]	
Palmer et al, 1995	10	21	3	9	0.0%	1.82 [0.36, 9.27]	
Park et al, 2016	4	20	3	10	0.0%	0.58 [0.10, 3.33]	
Stephenson et al, 1992	2	7	12	22	0.0%	0.33 [0.05, 2.10]	
Wang et al, 1992	3	14	3	4	0.0%	0.09 [0.01, 1.22]	
Yu et al, 2004	2	10	0	3	0.0%	2.06 [0.08, 54.80]	
Total (95% CI)		534		263	100.0%	0.63 [0.29, 1.34]	-
Total events	107		48				
Heterogeneity: Tau ² = 0.4	1; Chi ² = 10.30	df = 4 (P	= 0.04); l ² =	61%			
Test for overall effect: Z =	1.20 (P = 0.23)						0.01 0.1 1 10 10 Favours surgery within24h Favours surgery after 24h

Subgroup analysis: Studies published ≥2009

		in 24h		ter 24h		Odds Ratio	Odds Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
air et al, 2009	8	38	10	68	6.9%	1.55 [0.55, 4.33]	
alci et al, 2009	1	8	1	3	0.9%	0.29 [0.01, 6.91]	· · · · · · · · · · · · · · · · · · ·
oyer et al, 2009	23	32	1	1	0.8%	0.82 [0.03, 22.09]	
hao et al, 2013	20	90	15	31	9.0%	0.30 [0.13, 0.72]	
orona et al, 2016	6	18	0	2	0.9%	2.60 [0.11, 62.57]	
eorge et al, 2009	8	61	0	11	1.1%	3.65 [0.20, 67.92]	
iolena et al, 2011	471	4755	458	5203	30.4%	1.14 [1.00, 1.30]	-
luang et al, 2008	2	14	1	2	0.0%	0.17 [0.01, 3.89]	
luang et al, 2011	38	280	19	192	14.8%	1.43 [0.80, 2.56]	
aiser et al, 1981	6	17	2	3	0.0%	0.27 [0.02, 3.67]	
alaivani et al, 2012	10	35	5	25	5.2%	1.60 [0.47, 5.44]	
ee et al, 2014	12	81	6	19	5.8%	0.38 [0.12, 1.18]	
lawijn et al, Feb 2019	14	51	7	20	6.1%	0.70 [0.23, 2.12]	
gilvie et al, 2006	13	134	1	16	0.0%	1.61 [0.20, 13.21]	
almer et al, 1995	10	21	3	9	0.0%	1.82 [0.36, 9.27]	
ark et al, 2016	4	20	3	10	2.8%	0.58 [0.10, 3.33]	
tephenson et al, 1992	2	7	12	22	0.0%	0.33 [0.05, 2.10]	
ugihara et al, 2012	42	262	23	117	15.4%	0.78 [0.44, 1.37]	
Vang et al, 1992	3	14	3	4	0.0%	0.09 [0.01, 1.22]	
u et al, 2004	2	10	0	3	0.0%	2.06 [0.08, 54.80]	
otal (95% CI)		5731		5702	100.0%	0.92 [0.68, 1.25]	•
otal events	657		548				

Test for overall effect: Z = 0.53 (P = 0.60)



Subgroup analysis: Studies without limitation on affected body region by NSTI

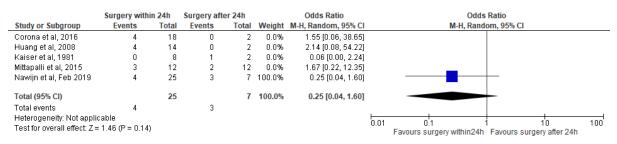
	Surgery with	in 24h	Surgery aft	er 24h		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Bair et al, 2009	8	38	10	68	12.7%	1.55 [0.55, 4.33]		
Balci et al, 2009	1	8	1	3	0.0%	0.29 [0.01, 6.91]		
Boyer et al, 2009	23	32	1	1	0.0%	0.82 [0.03, 22.09]		
Chao et al, 2013	20	90	15	31	15.3%	0.30 [0.13, 0.72]		
Corona et al, 2016	6	18	0	2	0.0%	2.60 [0.11, 62.57]		
George et al, 2009	8	61	0	11	2.5%	3.65 [0.20, 67.92]		
Huang et al, 2008	2	14	1	2	0.0%	0.17 [0.01, 3.89]		
Huang et al, 2011	38	280	19	192	20.8%	1.43 [0.80, 2.56]		+
Kaiser et al, 1981	6	17	2	3	3.1%	0.27 [0.02, 3.67]		
Kalaivani et al, 2012	10	35	5	25	10.2%	1.60 [0.47, 5.44]		
Lee et al, 2014	12	81	6	19	11.1%	0.38 [0.12, 1.18]		-
Nawijn et al, Feb 2019	14	51	7	20	11.6%	0.70 [0.23, 2.12]		
Ogilvie et al, 2006	13	134	1	16	4.5%	1.61 [0.20, 13.21]		
Palmer et al, 1995	10	21	3	9	0.0%	1.82 [0.36, 9.27]		
Park et al, 2016	4	20	3	10	6.1%	0.58 [0.10, 3.33]		
Stephenson et al, 1992	2	7	12	22	0.0%	0.33 [0.05, 2.10]		
Wang et al, 1992	3	14	3	4	0.0%	0.09 [0.01, 1.22]		
Yu et al, 2004	2	10	0	3	2.0%	2.06 [0.08, 54.80]		
Total (95% CI)		817		398	100.0%	0.85 [0.53, 1.38]		◆
Total events	135		68					
Heterogeneity: Tau ² = 0.2	20; Chi ² = 15.31,	df = 10 (P = 0.12); I ² =	35%			0.01	0.1 1 10 100
Test for overall effect: Z =							0.01	0.1 1 10 100 Favours surgery within24h Favours surgery after 24h
								Favours surgery within2411 Favours surgery alter 2411

	Surgery with	in 24h	Surgery aft	er 24h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bair et al, 2009	8	38	10	68	12.6%	1.55 [0.55, 4.33]	
Balci et al, 2009	1	8	1	3	1.3%	0.29 [0.01, 6.91]	· · · · · · · · · · · · · · · · · · ·
Boyer et al, 2009	23	32	1	1	1.2%	0.82 [0.03, 22.09]	
Chao et al, 2013	20	90	15	31	0.0%	0.30 [0.13, 0.72]	
Corona et al, 2016	6	18	0	2	1.3%	2.60 [0.11, 62.57]	
George et al, 2009	8	61	0	11	1.6%	3.65 [0.20, 67.92]	· · · · · · · · · · · · · · · · · · ·
Huang et al, 2008	2	14	1	2	1.3%	0.17 [0.01, 3.89]	·
Huang et al, 2011	38	280	19	192	39.1%	1.43 [0.80, 2.56]	- +
Kaiser et al, 1981	6	17	2	3	2.0%	0.27 [0.02, 3.67]	
Kalaivani et al, 2012	10	35	5	25	8.9%	1.60 [0.47, 5.44]	
Lee et al, 2014	12	81	6	19	0.0%	0.38 [0.12, 1.18]	
Nawijn et al, Feb 2019	14	51	7	20	10.9%	0.70 [0.23, 2.12]	
Ogilvie et al, 2006	13	134	1	16	3.0%	1.61 [0.20, 13.21]	
Palmer et al, 1995	10	21	3	9	5.0%	1.82 [0.36, 9.27]	
Park et al, 2016	4	20	3	10	4.4%	0.58 [0.10, 3.33]	
Stephenson et al, 1992	2	7	12	22	3.9%	0.33 [0.05, 2.10]	
Wang et al, 1992	3	14	3	4	2.0%	0.09 [0.01, 1.22]	· · · · · · · · · · · · · · · · · · ·
Yu et al, 2004	2	10	0	3	1.2%	2.06 [0.08, 54.80]	
Total (95% CI)		760		391	100.0%	1.11 [0.77, 1.60]	*
Total events	150		68				
Heterogeneity: Tau ² = 0.0		df= 15 (P = 0.63); P =	0%			
Test for overall effect: Z =							0.01 0.1 1 10 10
							Favours surgery within24h Favours surgery after 24h

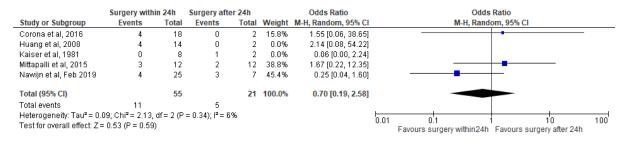
Surgery within 24 hours after presentation - amputation as outcome

	Surgery with	in 24h	Surgery after	r 24h		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% Cl	
Corona et al, 2016	4	18	0	2	12.6%	1.55 [0.06, 38.65]			
Huang et al, 2008	4	14	0	2	12.5%	2.14 [0.08, 54.22]			
Kaiser et al, 1981	0	8	1	2	10.0%	0.06 [0.00, 2.24]	←		
Mittapalli et al, 2015	3	12	2	12	30.1%	1.67 [0.22, 12.35]			-
Nawijn et al, Feb 2019	4	25	3	7	34.9%	0.25 [0.04, 1.60]			
Total (95% CI)		77		25	100.0%	0.63 [0.20, 2.05]			
Total events	15		6						
Heterogeneity: Tau ² = 0.	15; Chi ² = 4.34,	df = 4 (P	= 0.36); I ² = 89	6					
Test for overall effect: Z	= 0.76 (P = 0.45)					0.01	0.1 1 10 Favours surgery within24h Favours surgery a	

Subgroup analysis: High-quality studies



Subgroup analysis: Studies published ≥2009

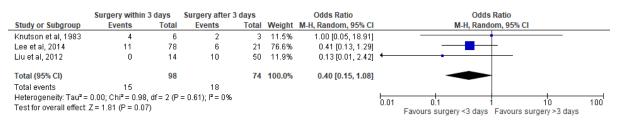


Subgroup analysis: Studies without limitation on affected body region by NSTI

	Surgery with	in 24h	Surgery after	er 24h		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
Corona et al, 2016	4	18	0	2	0.0%	1.55 [0.06, 38.65]]
Huang et al, 2008	4	14	0	2	0.0%	2.14 [0.08, 54.22]	1
Kaiser et al, 1981	0	8	1	2	17.4%	0.06 [0.00, 2.24]]
Mittapalli et al, 2015	3	12	2	12	39.4%	1.67 [0.22, 12.35]]
Nawijn et al, Feb 2019	4	25	3	7	43.1%	0.25 [0.04, 1.60]	
Total (95% CI)		45		21	100.0%	0.41 [0.08, 2.26]	
Total events	7		6				
Heterogeneity: Tau ² = 0.8	6; Chi ² = 3.22,	df = 2 (P	= 0.20); I ² = 3	8%			
Test for overall effect: Z =	1.02 (P = 0.31))					0.01 0.1 1 10 100 Favours surgery within24h Favours surgery after 24h

	Surgery with	in 24h	Surgery aft	er 24h		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Rando	om, 95% Cl	
Corona et al, 2016	4	18	0	2	15.6%	1.55 [0.06, 38.65]			•	
Huang et al, 2008	4	14	0	2	0.0%	2.14 [0.08, 54.22]				
Kaiser et al, 1981	0	8	1	2	12.5%	0.06 [0.00, 2.24]	←			
Mittapalli et al, 2015	3	12	2	12	33.7%	1.67 [0.22, 12.35]			-	
Nawijn et al, Feb 2019	4	25	3	7	38.1%	0.25 [0.04, 1.60]			_	
Total (95% CI)		63		23	100.0%	0.53 [0.14, 2.06]				
Total events	11		6							
Heterogeneity: Tau ² = 0.38; Chi ² = 3.71, df = 3 (P = 0.29); l ² = 19%										
Test for overall effect: Z	= 0.92 (P = 0.36)					0.01	0.1 1 Favours surgery within24h	10 Favours surgery after 24h	100

Surgery within 3 days after onset symptoms - mortality as outcome



Subgroup analysis: High-quality studies

	Surgery within	3 days	Surgery after	3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Knutson et al, 1983	4	6	2	3		Not estimable	
Lee et al, 2014	11	78	6	21	100.0%	0.41 [0.13, 1.29]	
Liu et al, 2012	0	14	10	50	0.0%	0.13 [0.01, 2.42]	
Total (95% CI)		78		21	100.0%	0.41 [0.13, 1.29]	
Total events	11		6				
Heterogeneity: Not ap	plicable					F	
Test for overall effect:	Z = 1.53 (P = 0.13)				U	0.01 0.1 1 10 100 Favours surgery <3 days Favours surgery >3 days

Subgroup analysis: Studies published ≥2009

	Surgery within	3 days	Surgery after 3	days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Knutson et al, 1983	4	6	2	3	0.0%	1.00 [0.05, 18.91]	
Lee et al, 2014	11	78	6	21	86.6%	0.41 [0.13, 1.29]	
Liu et al, 2012	0	14	10	50	13.4%	0.13 [0.01, 2.42]	·
Total (95% CI)		92		71	100.0%	0.35 [0.12, 1.02]	
Total events	11		16				
Heterogeneity: Tau ² =	0.00; Chi ² = 0.56,	df = 1 (P	= 0.45); I ² = 0%				
Test for overall effect:	Z = 1.92 (P = 0.05)					0.01 0.1 1 10 100 Favours surgery <3 days Favours surgery >3 days

Subgroup analysis: Studies without limitation on affected body region by NSTI

	Surgery within	3 days	Surgery after 3	days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	CI M-H, Random, 95% CI
Knutson et al, 1983	4	6	2	3	13.1%	1.00 [0.05, 18.91]]
Lee et al, 2014	11	78	6	21	86.9%	0.41 [0.13, 1.29]	aj <u> </u>
Liu et al, 2012	0	14	10	50	0.0%	0.13 [0.01, 2.42]	2]
Total (95% CI)		84		24	100.0%	0.46 [0.16, 1.34]	
Total events	15		8				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.31, df = 1 (P = 0.58); I ² = 0%							
Test for overall effect:							0.01 0.1 1 10 100 Favours surgery <3 days Favours surgery >3 days

	Surgery within	3 days	Surgery after	r 3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Knutson et al, 1983	4	6	2	3	0.0%	1.00 [0.05, 18.91]	
Lee et al, 2014	11	78	6	21	0.0%	0.41 [0.13, 1.29]	
Liu et al, 2012	0	14	10	50	100.0%	0.13 [0.01, 2.42] 👎	
Total (95% CI)		14		50	100.0%	0.13 [0.01, 2.42] -	
Total events	0		10				
Heterogeneity: Not ap						H	0.01 0.1 1 10 100
Test for overall effect:	Z = 1.36 (P = 0.17	7				0	Favours surgery <3 days Favours surgery >3 days

Hospital presentation within 3 days after onset symptoms - mortality as outcome

	Presentation within	1 3days	Presentation afte	r 3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Barupal et al, 2019	7	15	9	35	19.0%	2.53 [0.71, 8.97]	
Boyer et al, 2009	25	65	18	41	22.6%	0.80 [0.36, 1.77]	
Catena et al, 2004	1	4	6	7	8.3%	0.06 [0.00, 1.23]	← → → → → → → → → → → → → → → → → → → →
Ferretti et al, 2017	3	14	0	6	8.2%	3.96 [0.18, 89.19]	
Huang et al, 2008	1	14	2	2	7.1%	0.02 [0.00, 0.72]	← →
Knutson et al, 1983	5	8	1	1	7.1%	0.52 [0.02, 16.83]	
Lee et al, 2014	12	90	5	9	17.6%	0.12 [0.03, 0.52]	
Yu et al, 2004	1	6	2	9	10.1%	0.70 [0.05, 10.01]	
Total (95% CI)		216		110	100.0%	0.49 [0.16, 1.44]	
Total events	55		43				
Heterogeneity: Tau ² =	: 1.19; Chi ² = 17.11, d	f= 7 (P = 0					
Test for overall effect:	Z = 1.30 (P = 0.19)						0.01 0.1 1 10 100 Favours surgery <3 days Favours surgrery >3 days

Subgroup analysis: High-quality studies

	Presentation withi	n 3days	Presentation afte	r 3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Barupal et al, 2019	7	15	9	35	32.2%	2.53 [0.71, 8.97]	
Boyer et al, 2009	25	65	18	41	37.8%	0.80 [0.36, 1.77]	_
Catena et al, 2004	1	4	6	7	0.0%	0.06 [0.00, 1.23]	
Ferretti et al, 2017	3	14	0	6	0.0%	3.96 [0.18, 89.19]	
Huang et al, 2008	1	14	2	2	0.0%	0.02 [0.00, 0.72]	
Knutson et al, 1983	5	8	1	1		Not estimable	
Lee et al, 2014	12	90	5	9	30.0%	0.12 [0.03, 0.52]	_
Yu et al, 2004	1	6	2	9	0.0%	0.70 [0.05, 10.01]	
Total (95% CI)		170		85	100.0%	0.66 [0.15, 2.83]	
Total events	44		32				
Heterogeneity: Tau ² =	1.29; Chi ² = 9.56, df	= 2 (P = 0.	008); I² = 79%				
Test for overall effect:	Z = 0.56 (P = 0.58)	·					0.01 0.1 1 10 100 Favours surgery <3 days Favours surgery >3 days

Subgroup analysis: Studies published ≥2009

	Presentation withi	n 3days	Presentation after	3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Barupal et al, 2019	7	15	9	35	28.2%	2.53 [0.71, 8.97]	
Boyer et al, 2009	25	65	18	41	33.5%	0.80 [0.36, 1.77]	
Catena et al, 2004	1	4	6	7	0.0%	0.06 [0.00, 1.23]	
Ferretti et al, 2017	3	14	0	6	12.2%	3.96 [0.18, 89.19]	
Huang et al, 2008	1	14	2	2	0.0%	0.02 [0.00, 0.72]	
Knutson et al, 1983	5	8	1	1	0.0%	0.52 [0.02, 16.83]	
Lee et al, 2014	12	90	5	9	26.1%	0.12 [0.03, 0.52]	
Yu et al, 2004	1	6	2	9	0.0%	0.70 [0.05, 10.01]	
Total (95% CI)		184		91	100.0%	0.82 [0.22, 3.09]	
Total events	47		32				
Heterogeneity: Tau² =	1.20; Chi ² = 10.64, d	f= 3 (P = 0).01); I² = 72%				
Test for overall effect:	Z = 0.29 (P = 0.78)						0.01 0.1 1 10 100 Favours surgery <3 days Favours surgrery >3 days

Subgroup analysis: Studies without limitation on affected body region by NSTI

	Presentation withi	n 3days	Presentation afte	r 3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Barupal et al, 2019	7	15	9	35	27.6%	2.53 [0.71, 8.97]	
Boyer et al, 2009	25	65	18	41	0.0%	0.80 [0.36, 1.77]	
Catena et al, 2004	1	4	6	7	15.1%	0.06 [0.00, 1.23]	← ■+
Ferretti et al, 2017	3	14	0	6	0.0%	3.96 [0.18, 89.19]	
Huang et al, 2008	1	14	2	2	0.0%	0.02 [0.00, 0.72]	
Knutson et al, 1983	5	8	1	1	13.3%	0.52 [0.02, 16.83]	
Lee et al, 2014	12	90	5	9	26.3%	0.12 [0.03, 0.52]	
Yu et al, 2004	1	6	2	9	17.6%	0.70 [0.05, 10.01]	
Total (95% CI)		123		61	100.0%	0.41 [0.08, 2.13]	
Total events	26		23				
Heterogeneity: Tau ² =	2.10; Chi ² = 11.84, d	f= 4 (P = 0	0.02); I ² = 66%				
Test for overall effect:							0.01 0.1 1 10 100 Favours surgery <3 days Favours surgery >3 days

	Presentation within	1 3days	Presentation afte	r 3 days		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Barupal et al, 2019	7	15	9	35	29.6%	2.53 [0.71, 8.97]	
Boyer et al, 2009	25	65	18	41	41.5%	0.80 [0.36, 1.77]	
Catena et al, 2004	1	4	6	7	8.8%	0.06 [0.00, 1.23]	· · · · · · · · · · · · · · · · · · ·
Ferretti et al, 2017	3	14	0	6	8.8%	3.96 [0.18, 89.19]	
Huang et al, 2008	1	14	2	2	0.0%	0.02 [0.00, 0.72]	
Knutson et al, 1983	5	8	1	1	0.0%	0.52 [0.02, 16.83]	
Lee et al, 2014	12	90	5	9	0.0%	0.12 [0.03, 0.52]	
Yu et al, 2004	1	6	2	9	11.3%	0.70 [0.05, 10.01]	
Total (95% CI)		104		98	100.0%	1.01 [0.37, 2.74]	
Total events	37		35				
Heterogeneity: Tau ² =	0.47; Chi ² = 6.53, df =	= 4 (P = 0.					
Test for overall effect:		,					0.01 0.1 1 10 100 Favours surgery <3 days Favours surgrery >3 days
							Favours surgery <5 days Favours surgrery <5 days