

Supplementary material to:

The association between interleukin-6 inhibitors as treatment for COVID-19 and mental health problems in ICU survivors

Table S1

Psychiatric medications considered to define pre-intensive care unit mental health problems in the university medical center Utrecht follow-up cohort

Class	Drugs taken into account
Antidepressants	Imipramine, clomipramine, amitriptyline, nortriptyline, nortriphen, doxepine, sinequan, dosulepine, prothiaden, maprotiline, fluoxetine, Prozac, citalopram, cipramil, paroxetine, Seroxat, sertraline, Zoloft, fluvoxamine, fevarin, escitalopram, Lexapro, fenelzine, nardil, tranylcypromine, tracydal, moclobemide, aurorix, mianserine, tolvon, trazodone, trazolan, mirtazapine, Remeron, bupropion, Wellbutrin, venlafaxine, efexor, duloxetine, Cymbalta, agomelatine, valdoxan, vortioxetine, brintellix, mirtazepine
Antipsychotics	Flufenazine, perfenazine, periciazine, neuleptil, haloperidol, Haldol, broomperidol, impromen, droperidol, sertindol, serdolect, lurasidone, latuda, flupentixol, fluanxol, clopentixol, chloorprotixeen, Truxal, zuclopentixol, cisordinol, fluspirileen, imap, pimozide, penfluridol, acemap, clozapine, zaponex, leponex, olanzapine, Zyprexa, quetiapine, Seroquel, sulpiride, dogmatil, tiapride, amisulpride, aktiprol, risperidone, Risperdal, aripiprazole, ability, paliperidone, Invega, cariprazine, reagila, brexpiprazol, rxulti
Anxiolytics	Diazepam, chlordiazepoxide, oxazepam, seresta, lorazepam, bromazepam, clobazam, frisium, prazepam, reapam, alprazolam, xanax

Table S2*Patient characteristics divided by availability of outcome measurements*

	Overall n = 206	Study Population n = 170	Excluded (Any missing outcome) n = 36
Exposed to interleukin-6 inhibitor [†] , n (%)	145 (70.4)	119 (70.0)	26 (72.2)
Age in years, mean (SD)	59.7 (10.2)	60.1 (9.6)	57.9 (12.6)
Female, n (%)	71 (34.5)	62 (36.5)	9 (25.0)
BMI, median (IQR) ^a	28.7 (25.4 – 31.7)	29.0 (25.8 – 32.0)	27.3 (24.1 – 29.8)
Pre-ICU mental health problems, n (%) ^b	34 (16.5)	32 (18.8)	2 (5.6)
Pre-ICU use of psychiatric medication, n (%) ^c	38 (18.4)	33 (19.4)	5 (13.9)
Antidepressants, n (%)	19 (9.2)	18 (10.6)	1 (2.8)
Antipsychotics, n (%)	15 (7.3)	12 (7.1)	3 (8.3)
Anxiolytics, n (%)	14 (6.8)	12 (7.1)	2 (5.6)
ICU length of stay in days, median (IQR)	10 (6 – 18)	10 (7 – 18)	9 (5 – 16)
APACHE IV score, mean (SD)	64.5 (18.5)	65.0 (19.2)	62.1 (14.9)
SOFA on day 1, median (IQR)	5 (3 – 7)	5 (3 – 7)	5 (3 – 6)
Delta SOFA between day 1 and day 4 (or final day), mean (SD)	0.5 (3.2)	0.6 (3.4)	-0.1 (2.2)
Mechanical ventilation, n (%)	181 (87.9)	151 (88.8)	30 (83.3)
Propofol sedation, n (%)	165 (80.1)	137 (80.6)	28 (77.8)
Midazolam sedation, n (%)	144 (69.9)	121 (71.2)	23 (63.9)
Delirium during ICU admission, n (%) ^d	155 (75.2)	127 (74.7)	28 (77.8)
Glucocorticoids during ICU admission, n (%)	200 (97.1)	164 (96.5)	36 (100)

APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, ICU = Intensive Care Unit,

IL-6 = Interleukin-6, IQR = interquartile range, SD = standard deviation, SOFA = Sequential Organ Failure

Assessment

[†]Tocilizumab or sarilumab^a Missing for 4 (2%) patients^b Missing for 1 (0%) patient^c Missing for 4 (2%) patients^d Missing for 12 (6%) patients

Table S3

Sensitivity analysis on mental health problems at 3 months and exposure to interleukin-6 inhibitors (Radboudumc cohort only)

Composite outcome of mental health problems (PTSD, anxiety and/or depression)				
	Events/ total (n)	Absolute risk	Crude OR (95% CI)	Adjusted^a OR (95% CI)
IL-6 inhibitor	11 / 34	32%	1.04 (0.31 – 3.46)	1.02 (0.30 – 3.41)
No IL-6 Inhibitor	6 / 19	32%		
Post-traumatic stress disorder				
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted^a OR (95% CI)
IL-6 inhibitor	5 / 34	15%	1.47 (0.26 – 8.40)	1.36 (0.23 – 7.88)
No IL-6 Inhibitor	2 / 19	11%		
Anxiety				
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted^a OR (95% CI)
IL-6 inhibitor	7 / 34	21%	0.97 (0.24 – 3.87)	0.87 (0.21 – 3.59)
No IL-6 Inhibitor	4 / 19	21%		
Depression				
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted^a OR (95% CI)
IL-6 inhibitor	9 / 34	26%	1.01 (0.28 – 3.60)	1.00 (0.28 – 3.58)
No IL-6 Inhibitor	5 / 19	26%		

CI = confidence interval, IL-6 = interleukin-6, OR = odds ratio, PTSD = post-traumatic stress disorder

^a Adjusted for propensity scores estimated based on age, sex, body mass index, pre-intensive care unit (ICU) mental health problems, mechanical ventilation, Acute Physiology and Chronic Health Evaluation IV score, Sequential Organ Failure Assessment (SOFA) score on day 1, delta SOFA score between day 1 and day 4 (or the final ICU day if earlier), delirium during ICU admission and glucocorticoid use during ICU admission.

Table S4

Sensitivity analysis on mental health problems and exposure to interleukin-6 inhibitors stratified by treatment center (university medical center Utrecht and Radboudumc)

	University medicalcenter Utrecht				Radboudumc			
	Composite outcome of mental health problems (PTSD, anxiety and/or depression)							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	25 / 82	30%	0.50 (0.21 – 1.15)	0.45 (0.19 – 1.10)	10 / 37	27%	0.63 (0.19 – 2.07)	0.53 (0.15 – 1.85)
No IL-6 Inhibitor	15 / 32	47%			7 / 19	37%		
	Post-traumatic stress disorder							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	15 / 82	18%	0.43 (0.17 – 1.07)	0.45 (0.17 – 1.18)	6 / 37	16%	0.54 (0.14 – 2.08)	0.41 (0.10 – 1.76)
No IL-6 Inhibitor	11 / 32	34%			5 / 19	26%		
	Anxiety							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	20 / 82	24%	1.15 (0.43 – 3.06)	1.11 (0.40 – 3.08)	6 / 37	16%	0.54 (0.14 – 2.08)	0.33 (0.07 – 1.50)
No IL-6 Inhibitor	7 / 32	22%			5 / 19	26%		
	Depression							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	20 / 82	24%	0.71 (0.29 – 1.75)	0.74 (0.29 – 1.90)	9 / 37	24%	0.90 (0.25 – 3.20)	0.70 (0.18 – 2.70)
No IL-6 Inhibitor	10 / 32	31%			5 / 19	26%		

CI = confidence interval, IL-6 = interleukin-6, OR = odds ratio, PTSD = post-traumatic stress disorder,

^a Adjusted for propensity scores estimated based on age, sex, body mass index, pre-intensive care unit (ICU) mental health problems, mechanical ventilation, Acute Physiology and Chronic Health Evaluation IV score, Sequential Organ Failure Assessment (SOFA) score on day 1, delta SOFA score between day 1 and day 4 (or the final ICU day if earlier), delirium during ICU admission and glucocorticoid use during ICU admission.

Table S5

Sensitivity analysis on mental health problems and exposure to interleukin-6 inhibitors stratified by baseline CRP (<75 mg/L vs. ≥75 mg/L)

	Baseline CRP < 75 mg/L				Baseline CRP ≥ 75 mg/L			
	Composite outcome of mental health problems (PTSD, anxiety and/or depression)							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	5 / 18	28%	0.34 (0.08 – 1.43)	0.26 (0.04 – 1.92)	11 / 50	22%	0.52 (0.17 – 1.63)	0.41 (0.12 – 1.41)
No IL-6 Inhibitor	8 / 15	53%			7 / 20	35%		
	Post-traumatic stress disorder							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	2 / 18	11%	0.11 (0.02 – 0.65)	0.09 (0.01 – 0.97)	7 / 50	14%	0.92 (0.21 – 3.99)	0.88 (0.18 – 4.22)
No IL-6 Inhibitor	8 / 15	53%			3 / 20	15%		
	Anxiety							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	4 / 18	22%	0.57 (0.12 – 2.68)	0.40 (0.05 – 3.30)	8 / 50	16%	0.57 (0.16 – 2.02)	0.58 (0.15 – 2.27)
No IL-6 Inhibitor	5 / 15	33%			5 / 20	25%		
	Depression							
	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)	Events / total (n)	Absolute risk	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
IL-6 inhibitor	5 / 18	28%	1.06 (0.23 – 4.94)	0.49 (0.06 – 4.17)	9 / 50	18%	0.41 (0.13 – 1.31)	0.36 (0.10 – 1.28)
No IL-6 Inhibitor	4 / 15	27%			7 / 20	35%		

CI = confidence interval, CRP = C-reactive protein, IL-6 = interleukin-6, mg = milligram, OR = odds ratio, PTSD = post-traumatic stress disorder

^a Adjusted for propensity scores estimated based on age, sex, body mass index, pre-intensive care unit (ICU) mental health problems, mechanical ventilation, Acute Physiology and Chronic Health Evaluation IV score, Sequential Organ Failure Assessment (SOFA) score on day 1, delta SOFA score between day 1 and day 4 (or the final ICU day if earlier), delirium during ICU admission and glucocorticoid use during ICU admission.