

Table SI. Simple regression analyses to identify determinants of the Δ NRS on day 1 in the Morphine and Oxycodone groups.

Variable	Morphine (n=70)				Oxycodone (n=68)			
	β	t-value	Partial regression coefficient (95% CI)	P-value	β	t-value	Partial regression coefficient (95% CI)	P-value
Age	-0.02	-0.19	0.85 (-0.53 to 0.43)	0.851	0.04	0.30	0.76 (-0.33 to 0.44)	0.764
Sex	-0.03	-0.22	-0.05 (-0.54 to 0.44)	0.828	-0.12	-0.95	-0.18 (-0.57 to 0.21)	0.345
Performance status	-0.07	-0.60	-0.15 (-0.64 to 0.3)	0.549	0.22	1.84	0.36 (-0.03 to 0.75)	0.070
Pre-NRS score	0.58	5.81	0.55 (0.36 to 0.74)	<0.0001	0.60	6.11	0.47 (0.32 to 0.63)	<0.0001
HADS score	0.07	0.59	0.02 (-0.04 to 0.08)	0.555	0.15	1.19	0.03 (-0.02 to 0.09)	0.237
SF-MPQ-2 score	0.26	2.26	0.02 (-0.00 to 0.03)	0.027	0.29	2.42	0.01 (0.002 to 0.02)	0.018
Dose of opioid	-0.16	-1.38	-0.33 (-0.81 to 0.15)	0.174	-0.15	-1.22	-0.28 (-0.74 to 0.18)	0.228
Chemokines/cytokines ^a								
CCL1	0.01	0.05	0.01 (-0.47 to 0.49)	0.957	-0.05	-0.44	-0.08 (-0.47 to 0.30)	0.663
CCL2	0.11	0.88	0.22 (-0.28 to 0.71)	0.312	-0.06	-0.48	-0.01 (-0.49 to 0.30)	0.631
CCL3	0.003	0.03	0.01 (-0.48 to 0.494)	0.970	-0.17	-1.41	-0.27 (-0.66 to 0.11)	0.163
CCL7	0.21	1.73	0.45 (-0.07 to 0.97)	0.088	0.05	0.42	0.09 (-0.35 to 0.54)	0.676
CCL8	-0.21	-1.76	-0.41 (-0.88 to 0.06)	0.084	-0.03	-0.21	-0.04 (-0.42 to 0.34)	0.836
CCL11	-0.01	-0.12	-0.03 (-0.53 to 0.47)	0.909	-0.17	-1.42	-0.28 (-0.68 to 0.11)	0.161
CCL13	-0.01	-0.09	-0.02 (-0.51 to 0.46)	0.932	0.09	0.74	0.14 (-0.24 to 0.53)	0.463
CCL15	0.17	1.40	0.33 (-0.14 to 0.81)	0.166	-0.04	-0.36	-0.07 (-0.45 to 0.31)	0.719
CCL17	0.14	1.15	0.29 (-0.21 to 0.80)	0.255	-0.06	-0.47	-0.10 (-0.51 to 0.32)	0.641
CCL19	0.02	0.15	0.04 (-0.45 to 0.52)	0.878	-0.04	-0.35	-0.07 (-0.46 to 0.32)	0.730
CCL20	0.18	1.50	0.36 (-0.12 to 0.83)	0.138	-0.12	-1.02	-0.20 (-0.58 to 0.19)	0.314
CCL21	-0.03	-0.24	-0.06 (-0.56 to 0.44)	0.812	-0.07	-0.56	-0.11 (-0.52 to 0.29)	0.580
CCL22	0.03	0.28	0.07 (-0.41 to 0.55)	0.781	-0.07	-0.55	-0.11 (-0.49 to 0.28)	0.586
CCL23	0.08	0.64	0.15 (-0.33 to 0.64)	0.525	-0.03	-0.24	-0.05 (-0.43 to 0.34)	0.813
CCL24	0.14	1.14	0.27 (-0.20 to 0.75)	0.260	-0.16	-1.31	-0.25 (-0.63 to 0.13)	0.195

CCL25	0.003	0.02	0.01 (-0.48 to 0.50)	0.981	-0.05	-0.37	-0.07 (-0.47 to 0.32)	0.714
CCL26	0.14	1.14	0.26 (-0.21 to 0.79)	0.258	-0.03	-0.23	-0.05 (-0.45 to 0.36)	0.817
CCL27	0.08	0.66	0.16 (-0.32 to 0.64)	0.514	-0.05	-0.42	-0.08 (-0.46 to 0.30)	0.675
CX3CL1	0.15	1.25	0.30 (-0.18 to 0.77)	0.215	-0.15	-1.26	-0.24 (-0.62 to 0.14)	0.211
CXCL1	-0.07	-0.56	-0.15 (-0.69 to 0.39)	0.577	0.01	0.07	0.01 (-0.43 to 0.46)	0.947
CXCL2	-0.05	-0.10	0.24 (-0.58 to 0.38)	0.685	0.14	1.18	0.23 (-0.16 to 0.61)	0.241
CXCL5	-0.08	-0.64	-0.16 (-0.67 to 0.35)	0.527	-0.02	-0.19	-0.04 (-0.45 to 0.37)	0.854
CXCL6	0.03	0.26	0.07 (-0.43 to 0.56)	0.793	-0.08	-0.68	-0.14 (-0.53 to 0.26)	0.496
CXCL9	0.06	0.52	0.13 (-0.35 to 0.61)	0.597	-0.08	-0.68	-0.13 (-0.51 to 0.25)	0.497
CXCL10	-0.01	-0.07	-0.02 (-0.50 to 0.46)	0.945	-0.04	-0.33	-0.06 (-0.48 to 0.32)	0.743
CXCL11	0.005	0.04	0.01 (-0.47 to 0.49)	0.969	-0.05	-0.39	-0.08 (-0.46 to 0.31)	0.696
CXCL12	0.03	0.27	0.07 (-0.42 to 0.55)	0.787	-0.09	-0.77	-0.19 (-0.54 to 0.24)	0.444
CXCL13	-0.08	-0.68	-0.16 (-0.65 to 0.32)	0.498	-0.11	-0.86	-0.17 (-0.55 to 0.22)	0.394
CXCL16	0.12	1.00	0.24 (-0.24 to 0.72)	0.320	-0.12	-0.97	-0.19 (-0.57 to 0.20)	0.335
IFN- γ	0.20	1.66	0.46 (-0.09 to 1.00)	0.102	-0.08	-0.64	-0.14 (-0.58 to 0.30)	0.523
IL-1 β	0.004	0.03	0.01 (-0.48 to 0.49)	0.973	-0.10	-0.79	-0.15 (-0.53 to 0.23)	0.431
IL-2	0.19	1.59	0.42 (-0.11 to 0.94)	0.117	-0.12	-0.97	-0.20 (-0.61 to 0.21)	0.335
IL-4	-0.11	-0.91	-0.23 (-0.75 to 0.28)	0.367	0.02	0.19	0.04 (-0.38 to 0.46)	0.847
IL-6	0.11	0.90	0.21 (-0.26 to 0.69)	0.373	0.12	0.96	0.18 (-0.20 to 0.57)	0.339
IL-8	0.04	0.30	0.07 (-0.41 to 0.55)	0.767	-0.05	-0.42	-0.08 (-0.46 to 0.30)	0.975
IL-10	-0.01	-0.09	-0.02 (-0.51 to 0.46)	0.928	-0.06	-0.50	-0.10 (-0.49 to 0.29)	0.617
IL-16	0.12	1.00	0.25 (-0.24 to 0.73)	0.319	-0.30	-2.56	-0.48 (-0.85 to -0.11)	0.013
MIF	0.23	1.93	0.45 (-0.02 to 0.92)	0.058	0.07	0.62	0.12 (-0.26 to 0.51)	0.535
TNF- α	-0.02	-0.19	-0.05 (-0.53 to 0.43)	0.851	-0.03	-0.27	-0.05 (-0.44 to 0.33)	0.790

^aFor each chemokine/cytokine, patients with concentrations over and under the median concentrations were compared. Δ NRS, difference in the score on the numerical rating scale recorded prior to the start of opioid treatment and after opioid dose titration; CI, confidence interval; pre-NRS score, pre-treatment score on the numerical rating scale; HADS score, total score on the Hospital Anxiety and Depression Scale; SF-MPQ-2 score, total score on the Short-Form McGill Pain

Questionnaire-2; For abbreviations of the chemokines and cytokines, see Table II; β standardized partial regression coefficients for "<70" (Age), "male" (Sex), "0 and 1" (Performance status), "Low" (Dose for opioid). These β values represent the standardized partial regression coefficients for the "higher concentration group."

Table SII. Lists of genotypes and haplotypes of the 2 SNPs of the IL-16 gene.

A, Genotype		
rs4778889 (T/C)	rs11556218 (T/G)	n (138)
TT	TT	88
TT	TG	0
TT	GG	0
TC	TT	14
TC	TG	30
TC	GG	0
CC	TT	1
CC	TG	1
CC	GG	4
B, Haplotype		
rs4778889 (T/C)	rs11556218 (T/G)	n (276)
T	T	220
T	G	0
C	T	17
C	G	39

Table SIII. Independent determinants of the Δ NRS on day 1 in the overall subject population (N = 138) (simple regression model)

Variable	β	t-value	Partial regression coefficient (95% CI)	P-value
Age	-0.003	-0.04	-0.01 (-0.31 to 0.30)	0.970
Sex	-0.07	-0.81	-0.13 (-0.43 to 0.18)	0.421
Performance status	0.06	0.64	0.10 (-0.21 to 0.42)	0.523
Pre-NRS score	0.58	8.4	0.52 (0.39 to 0.64)	<0.0001
HADS score	0.10	1.14	0.02 (-0.02 to 0.07)	0.256
SF-MPQ-2 Total score	0.27	3.32	0.01 ((0.01 to 0.02)	0.001
Treatment ^a	-0.07	-0.84	-0.13 (-0.43 to 0.17)	0.400
Genotype				
IL-16 (rs4778889)	-0.12	-1.35	-0.21 (-0.53 to 0.10)	0.178
IL-16 (rs11556218)	-0.17	-2.56	-0.44 (-0.78 to -0.10)	0.012
CCL11 (rs17809012)	-0.21	-2.56	-0.44 (-0.78 to -0.10)	0.018

^amorphine or oxycodone. Δ NRS, difference in the score on the numerical rating scale recorded prior to the start of opioid treatment and after opioid titration; CI, confidence interval; VIF, variance inflation factor; pre-NRS score, pre-treatment score on the numerical rating scale; HADS score, total score on the Hospital Anxiety and Depression Scale; SF-MPQ-2 score, total score on the Short-Form McGill Pain Questionnaire-2; IL-16, interleukin 16; CCL11, C-C motif chemokine ligand 11. β standardized partial regression coefficient for "<70" (Age), "male" (Sex), "0 and 1" (Performance status), "morphine" (Treatment), "TT" for rs4778889, "TT" for rs11556218 and "AA" for rs17809012 (Genotype).

Table SIV. Independent determinants of the Δ NRS on day 1 in the overall subject population (N = 138) (Multiple regression model).

Variable	Multiple regression model 1					Multiple regression model 2				
	β	t-value	Partial regression coefficient (95% CI)	P-value	VIF	β	t-value	Partial regression coefficient (95% CI)	P-value	VIF
Age	0.07	0.93	0.12 (-0.14 to 0.38)	0.352	1.09	0.07	0.91	0.12 (-0.14 to 0.37)	0.363	1.09
Sex	-0.10	-1.33	-0.17 (-0.43 to 0.08)	0.184	1.09	-0.08	-1.14	-0.14 (-0.40 to 0.11)	0.258	1.10
Performance status	0.02	0.21	0.03 (-0.25 to 0.31)	0.835	1.17	0.01	0.09	0.01 (-0.26 to 0.29)	0.931	1.18
Pre-NRS score	0.56	7.31	0.49 (0.36 to 0.63)	<0.0001	1.22	0.54	7.13	0.48 (0.35 to 0.61)	<0.0001	1.24
HADS score	-0.01	-0.19	-0.003 (-0.004 to 0.01)	0.852	1.33	-0.02	-0.30	-0.01 (-0.04 to 0.03)	0.852	1.33
SF-MPQ-2 Total score	0.09	1.11	0.005 (-0.004 to -0.01)	0.267	1.47	0.11	1.30	0.005 (-0.003 to -0.01)	0.198	1.48
Treatment ^a	-0.04	-0.56	-0.07 (-0.33 to 0.19)	0.574	1.11	-0.02	-0.23	-0.03 (-0.29 to 0.23)	0.821	1.12
Genotype										
IL-16 (rs4778889)	-0.08	-1.07	-0.14 (-0.40 to 0.12)	0.286	1.03					
IL-16 (rs11556218)						-0.15	-2.08	-0.31 (-0.60 to -0.01)	0.040	1.10
CCL11 (rs17809012)	-0.14	-1.98	-0.25 (-0.50 to -0.0005)	0.049	1.03	-0.16	-2.22	-0.28 (-0.53 to -0.03)	0.028	1.05

^amorphine or oxycodone. Δ NRS, difference in the score on the numerical rating scale recorded prior to the start of opioid treatment and after opioid titration; CI, confidence interval; VIF, variance inflation factor; pre-NRS score, pre-treatment score on the numerical rating scale; HADS score, total score on the Hospital Anxiety and Depression Scale; SF-MPQ-2 score, total score on the Short-Form McGill Pain Questionnaire-2; IL-16, interleukin 16; CCL11, C-C motif chemokine ligand 11. β standardized partial regression coefficient for "<70" (Age), "male" (Sex), "0 and 1" (Performance status), "morphine" (Treatment), "TT" for rs4778889, "TT" for rs11556218 and "AA" for rs17809012 (Genotype).

Table SV. Multiple regression analysis to test the interaction with treatment for each variable.

Variable	β	t-value	Partial regression coefficient (95% CI)	VIF	P-value
Age	0.04	0.43	0.07 (-0.24 to 0.37)	1.00	0.667
Treatment	-0.07	-0.83	-0.13 (-0.44 to 0.18)	1.01	0.405
Age*treatment	0.005	0.06	0.008 (-0.30 to 0.32)	1.01	0.956
Sex	-0.07	-0.76	-0.12 (-0.43 to 0.19)	1.00	0.450
Treatment	-0.07	-0.85	-0.13 (-0.44 to 0.18)	1.02	0.399
Sex*treatment	0.04	0.41	0.06 (-0.24 to 0.37)	1.02	0.680
PS	0.06	0.67	0.11 (-0.21 to 0.42)	1.00	0.506
Treatment	-0.03	-0.36	-0.06 (-0.37 to 0.26)	1.08	0.721
PS*treatment	-0.14	-1.61	-0.26 (-0.57 to 0.06)	1.08	0.110
Pre-NRS score	0.58	8.29	0.51 (0.39 to 0.63)	1.00	<.0001
Treatment	-0.05	-0.74	-0.09 (-0.354 to 0.15)	1.00	0.458
Pre-NRS*treatment	0.05	0.65	0.04 (-0.08 to 0.16)	1.00	0.517
HADS score	0.13	1.53	0.03 (-0.01 to 0.07)	1.01	0.129
Treatment	-0.08	-0.96	-0.15 (-0.45 to 0.16)	1.01	0.339
HADS*treatment	-0.01	-0.16	-0.003 (-0.04 to 0.04)	1.01	0.877
SF-MPQ-2 score	0.29	3.27	0.01(0.005 to 0.023)	1.15	0.001
Treatment	-0.01	-0.09	-0.01 (-0.32 to 0.29)	1.06	0.930
SF-MPQ-2*treatment	0.07	0.75	0.002 (-0.007 to 0.01)	1.09	0.453
IL-16 (rs4778889)	-0.11	-1.32	-0.21 (-0.53 to 0.10)	1.00	0.188
Treatment	-0.11	-1.20	-0.19 (-0.51 to 0.12)	1.09	0.234
IL-16*treatment	0.10	1.17	0.19 (-0.13 to -0.50)	1.08	0.246
IL-16 (rs11556218)	-0.21	-2.52	-0.44 (-0.78 to -0.09)	1.02	0.013
Treatment	-0.05	-0.05	-0.09 (-0.43 to 0.26)	1.36	0.617

IL-16*treatment	0.001	-0.01	-0.001 (-0.35 to 0.34)	1.31	0.993
CCL11 (rs17809012)	-0.11	-1.30	-0.20 (-0.49 to 0.10)	1.01	0.197
Treatment	-0.07	-0.85	-0.13 (-0.43 to 0.17)	1.01	0.399
CCL11 *treatment	-0.20	-2.39	-0.36 (-0.66 to -0.06)	1.00	0.018
rs4778889/rs17809012 (I) ^a	-0.15	-1.82	-0.30 (-0.62 to -0.03)	1.00	0.071
Treatment	-0.13	-1.39	-0.23 (-0.55 to 0.10)	1.17	0.166
(I)*treatment	-0.14	-1.49	-0.24 (-0.57 to 0.08)	1.17	0.140
rs4778889/rs17809012 (II) ^b	0.09	1.13	0.18 (-0.13 to 0.49)	1.00	0.262
Treatment	0.03	0.35	0.06 (-0.26 to 0.37)	1.14	0.724
(II)*treatment	0.29	3.30	0.52 (0.21 to 0.83)	1.14	0.001
rs4778889/rs17809012 (III) ^c	0.03	0.33	0.06 (-0.31 to 0.44)	1.01	0.741
Treatment	-0.14	-1.37	-0.26 (-0.63 to 0.11)	1.52	0.172
(III)*treatment	-0.13	-1.22	-0.23 (-0.60 to 0.14)	1.51	0.225
rs4778889/rs17809012 (IV) ^d	0.07	0.71	0.16 (-0.29 to 0.60)	1.11	0.481
Treatment	-0.17	-1.36	-0.31 (-0.75 to 0.14)	2.14	0.177
(IV)*treatment	-0.13	-1.02	-0.23 (-0.68 to 0.21)	2.13	0.308
rs11556218/rs17809012 (I) ^e	-0.14	-1.65	-0.26 (-0.58 to 0.05)	1.00	0.101
Treatment	-0.10	-1.18	-0.19 (-0.50 to 0.13)	1.09	0.239
(I)*treatment	-0.13	-1.46	-0.23 (-0.54 to 0.08)	1.09	0.147
rs11556218/rs17809012 (II) ^f	-0.01	-0.10	-0.02 (-0.32 to 0.21)	1.01	0.919
Treatment	-0.02	-0.28	-0.04 (-0.35 to 0.26)	1.06	0.778
(II)*treatment	0.20	2.32	0.36 (0.05 to 0.67)	1.06	0.022
rs11556218/rs17809012 (III) ^g	0.01	0.10	0.02 (-0.40 to 0.45)	1.09	0.924
Treatment	-0.17	-1.39	-0.30 (-0.72 to 0.13)	1.95	0.168
(III)*treatment	-0.14	-1.19	-0.26 (-0.68 to 0.17)	1.93	0.234
rs11556218/rs17809012 (IV) ^h	0.19	2.26	0.59 (0.07 to 1.10)	1.01	0.025

Treatment	-0.07	-0.45	0.12 (-0.63 to 0.40)	2.95	0.651
(IV)*treatment	0.01	0.09	0.02 (-0.49 to 0.54)	2.95	0.931

A*B denotes the interaction between A and B. ^{a-d}Show a comparison of patients having a combination of genotypes (rs4778889/rs17809012): ^a"TT"/"AA" with those having other genotype combinations; ^b"TT"/("AG/GG") with others; ^c("TC/CC")/"AA" with others; ^d("TC/CC")/("AG/GG") with others. ^{e-h}Show a comparison of patients having a combination of genotypes (rs11556218/rs17809012): ^e"TT"/"AA" with those having other combinations; ^f"TT"/ ("AG/GG") with those having others; ^g("TG/GG")/"AA" with others; ^h("TG/GG")/("AG/GG") with others. Treatment denotes morphine or oxycodone. In each triad, relationships with a variable, treatment (morphine or oxycodone) and their interaction were estimated. CI, confidence interval; VIF, variance inflation factor; PS, performance status; pre-NRS score, pre-treatment score on the numerical rating scale ; HADS score, total score on the Hospital Anxiety and Depression Scale ; SF-MPQ-2 score, total score on the Short-Form McGill Pain Questionnaire-2; IL-16, interleukin 16; CCL11, C-C motif chemokine ligand 11.

Table SVI. Cancer types of the patients.

Cancer type, n (%)	Group M (n=70)	Group O (n=69) ^a
Lung	27 (38.6)	19 (27.5)
Breast	6 (8.6)	15 (21.7)
Colon	5 (7.1)	6 (8.7)
Head and neck	8 (11.4)	4 (5.8)
Esophageal	7 (10)	3 (4.3)
Gastric	3 (4.3)	4 (5.8)
Primary unknown	3 (4.3)	5 (7.2)
Pancreas	3 (4.3)	3 (4.3)
Mesothelioma	1 (1.4)	4 (5.8)
Gallbladder/bile duct	1 (1.4)	3 (4.3)
Others	6 (8.6)	3 (4.3)

^aIncluding one patient who was excluded from the current study because of insufficient clinical data. Group M, morphine group; Group O, oxycodone group.