Prevalence, Trajectory and Predictors of Post Stroke Pain

Prevalence, Trajectory and Predictors of Post Stroke Pain: Retrospective Analysis of Pooled Clinical Trial Datasets

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Short title: Prevalence, and Predictors of Post Stroke Pain

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Abstract

Background: Post-stroke pain remains under-diagnosed and inadequately managed. To inform the optimum time to initiate interventions, we examined prevalence, trajectory and participant factors associated with post-stroke pain.

Methods: Eligible studies from the Virtual International Stroke Trials Archives (VISTA) included an assessment of pain. Analyses of individual participant data (IPD) examined demography, pain, mobility, independence, language, anxiety/depression and vitality. Pain assessments were standardised to the European Quality of Life Scale [EQ-5D-3L] pain-domain, describing no, moderate or extreme pain. We described pain prevalence, and associations between participant characteristics and pain using multivariable models.

Results: From 94 studies (n>48,000 individual participant data [IPD]) in VISTA, 10 (n=10,002 IPD) included a pain assessment. Median age was 70.0 years (IQR [59.0,77.1]), 5,560 (55.6%) were male, baseline stroke-severity was NIHSS 10 (IQR [7,15]). Reports of extreme pain ranged between 3%-9.5% and was highest beyond 2 years post-stroke (31/328 [9.5%]); pain trajectory varied by study. Poorer independence was significantly associated with presence of moderate or extreme pain (5weeks-3months OR=1.5, 95%CI [1.4, 1.6]; 4-6months OR=1.7 95%CI [1.3, 2.1]; >6months OR=1.5, 95%CI [1.2, 2.0]), and increased severity of pain (5weeks-3months: OR=1.2, 95%CI [1.1,1.2]; 4-6months OR=1.1; 95%CI [1.1, 1.2]; >6months, OR=1.2, 95%CI [1.1, 1.2]), after adjusting for covariates. Anxiety/depression and lower vitality were each associated with pain severity.

Conclusions: Between 3%-9.5% of participants reported extreme post-stroke pain; presence and severity of pain were independently associated with dependence at each time point. Future studies could determine whether and when interventions may reduce prevalence and severity of post-stroke pain.

53 Non-standard Abbreviations and Acronyms

Abbreviation	Description
VISTA	Virtual International Stroke Trials Archives
IPD	Individual Participant Data
EQ-5D-3L	European Quality of Life Scale 3 -Level
IQR	Interquartile Range
NIHSS	National Institutes of Health Stroke Scale
CPSP	Central Post-Stroke Pain
ADL	Activities of Daily Living
QoL	Quality of Life
SF-36	RAND 36 Item Health Survey 1.0
NPRS	Numeric Pain Rating Scale
EQ-5D-5L	European Quality of Life Scale 5 -Level

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Introduction

Post-stroke pain is common[1] with prevalence between 10%[2] and 70%[3–5], and is poorly understood[6]. Pain has been reported by 48% of stroke survivors at 1 year[7], and persistent shoulder pain has been reported by 20% of people at 4 years[8]. Aetiology can be mixed but includes central post-stroke pain (CPSP)[9], headaches, and musculoskeletal issues often arising from post-stroke impairments,[2,9] commonly affecting the shoulder[1,10]. With increasing numbers surviving stroke with long-term impairments, the number of people with post-stroke pain will also increase[11], impacting on rehabilitation needs.

Pain is associated with poor outcomes including restricted mobility[12] and activities of daily living (ADL)[13], poorer participation in rehabilitation[14,15], decreased quality of life (QoL)[16], presence of depression[17] and fatigue[18]. QoL and recovery were each rated poorer in those who experienced frequent post-stroke pain, compared to those who experienced less frequent pain[19].

Despite the impact on everyday life, pain is under-diagnosed and inadequately managed[12], with other interventions prioritised [20]. A 5-year follow up study reported that a quarter of participants had unmet pain management needs[19], while up to two thirds of those who identified central pain following stroke reported inadequate intervention for their pain[16]. Management is further hindered by the different aetiologies of post-stroke pain, and a paucity of available treatment guidelines[21]. Nevertheless, the causes and factors associated with frequent occurrence of pain can be managed[19], and good pain management has been linked with functional improvement and better QoL[22], highlighting the importance of monitoring and developing interventions for post-stroke pain [19].

Monitoring post-stroke pain is complex as pain may coexist with complications such as fatigue or depression[22]. Additionally, stroke-related communication, cognition, perceptual, visual or upper limb impairments can hinder a person's ability to express pain or participate in a self-rated assessment[2,10]. Further, pain may be exacerbated by post-stroke consequences such as impaired motor function, and problems with gait, balance and posture[23], or influenced by pre-existing age-related pain such as arthritis. Information on pain symptoms is also not commonly volunteered,

particularly in elderly populations[24], thereby necessitating active enquiries about pain by clinicians. Post-stroke pain can therefore be overlooked by healthcare professionals [12].

Examination of data across the stroke recovery continuum and different recruitment settings would increase the generalisability of findings to the wider population. Further, to inform treatments for pain, we need a better understanding of assessment and epidemiology. Future pain intervention studies would benefit from estimates of post-stroke pain prevalence across the recovery continuum, information on patient characteristics associated with pain, and prognostic models of the natural history of pain progression.

Aims

We sought to describe the prevalence of, populations affected by, trajectory of and participant-related factors associated with post-stroke pain.

Methods

Data Availability: Data are available upon request to the Virtual Trials Archive vista.coordinator@glasgow.ac.uk. R scripts for data processing and analysis are available at https://github.com/hollytibble/Stroke_Pain.

Data

We conducted retrospective analyses of pooled, anonymised individual participant data (IPD) from the Virtual International Stroke Trials Archive (VISTA)[25]. IPD were included where participants had at least one assessment of pain reported during the study, using the pain domain of the European Quality of Life Scale (EQ-5D) 3 Level/ 5 Level scale, the pain domain of the RAND 36 Item Health Survey 1.0 item 21 (SF-36)[26] or the 0-10 Numeric Pain Rating Scale (NPRS). Data on demography, mobility using the Barthel Index (BI), independence using the modified Rankin scale (mRS), presence of a

language impairment (aphasia), stroke severity, medical history, fatigue, anxiety or depression (anxiety/depression) were extracted.

We defined language impairment as a score of ≥1 on the Best Language domain of the National Institutes of Health Stroke Scale (NIHSS) at baseline. Anxiety or depression was defined as a score of 2 or 3 on the anxiety/depression scale of the EQ-5D-3L and a score of 2 to 5 on the EQ-5D-5L scale. Fatigue was described according to a composite of items 23,27,29 and 31 of the SF-36 scale, as per scoring guidelines. An acute setting was defined as enrolment within 24 hours of stroke onset, a non-acute setting was described as enrolment >1 month from stroke onset, while mixed settings included enrolment within 7 days to 1-month post-stroke. Time since stroke onset was categorised *a priori* as 0 to 4 weeks, 5 weeks to 3 months, 4 to 6 months and >6 months. Where more detailed analyses of later time points were required, we described time points as 6 to 12 months, >1 to 2 years, and >2 years post-stroke.

Pain was defined pragmatically to consider the range of scoring conventions. "Some" pain was defined as a score above the scale minimum (minimum scoring =no pain on all assessment tools), and "extreme" pain as a maximum score on each of the assessment tools. Mobility using the BI mobility domain was transformed into a linear score to account for different scoring methods within studies, and combining wheelchair independence and independence, such that scores from studies reporting mobility on a 0-3 scale were multiplied by 5 to form a 0-15 score. We then allocated scores of 0->1, 10->2, and both 5 and 15 became 3. Thus, mobility was described on a linear 1-3 scale.

Pain Data Transformation

To facilitate analyses and interpretation of data on a single, clinically meaningful pain scale, we used a transformation algorithm previously adapted from the Early Breast Cancer Trialists Collaboration for use in a post-stroke aphasia population[27,28,29]. Briefly, we identified the most commonly used assessment tool and designated this as an "anchor measure," to which all other pain measures were transformed (matching value ranges for the anchor measure but preserving the

129 original scores' distributions). Therefore, all usable pain data were pooled and presented using a
130 clinically relevant assessment scale as a reference point.

131 Data from the SF-36, EQ-5D-5L, and 0-10 NPRS were transformed to fit the range of the EQ-
132 5D-3L pain domain (anchor measure). Patients in whom the 0-10 NPRS was assessed also had pain
133 assessments available using the EQ-5D-3L and 5L, which enabled us explore this transformation in the
134 context of a post-stroke pain population.

135 ***Analyses***

136 Transformation Validation

137 Where pain assessments using different tools were present for the same participant, the
138 transformed pain values were compared to the anchor measure values recorded on the same day.
139 Spearman correlation coefficients were calculated between the transformed pain values and the
140 anchor measure score, and between the original pain assessment value and the anchor measure
141 score.

142 Population Description

143 We described the demography of the participants in our dataset using summary statistics. We
144 compared participant characteristics for those with no or moderate pain (EQ-5D-3L=1 or 2) and those
145 with extreme pain (EQ-5D-3L=3) using Mann-Whitney and χ^2 tests, as appropriate.

146 Prevalence and Trajectory of Pain

147 We described the number of participants with "some" pain, and with extreme pain (both
148 stratified by assessment tool), in each time period. Trajectories of pain were described for participants
149 with multiple measurements of pain within the first year since the onset of stroke.

150 Factors Associated with Post-Stroke Pain

151 We used logistic regression to investigate the factors associated with presence of moderate
152 or extreme pain, and extreme pain alone, stratified by time period, and recruitment setting. Factors
153 included participants' age, sex, initial stroke severity, mobility problems, diabetes, baseline aphasia,

and independence (median value by time period). If coefficients over 1000 or under 0.001 were observed due to small numbers, the variable was removed to improve model fit.

We used linear regression to investigate associations between participant factors and the reported pain severity. Where a participant had multiple pain measurements in the same time period, the median pain value was used. The linearity of the association with pain was tested for the continuous features (age, initial stroke severity, and independence) for each time-period and if the assumption was not held then they were converted to categorical variables. The variance of pain across the range of each continuous feature was assessed to confirm homoscedasticity.

Pain, Anxiety/Depression and Fatigue

Linear regression models examined associations between pain severity (1=no pain, 2=moderate pain, 3=extreme pain) and anxiety/depression on the EQ-5D. Where a participant had multiple measurements in the same time period, the median values were used. Finally, we examined associations between fatigue and pain using the Spearman correlation coefficient.

Results

From 94 studies comprising >48,000 IPD in VISTA, 10 studies included an assessment of pain (figure S1); 2 studies used a pain-specific assessment, and 8 captured pain in multidomain assessments.

Pain Measurement Transformations in the Post-Stroke Pain Population

One study used both EQ-5D-3L and the 0-10 NPRS. The values of the 0-10 NPRS (n=1064) transformed to fit the range of the EQ-5D-3L were compared to the originally recorded EQ-5D-3L values. The median difference between the observed EQ-5D-3L pain score and the transformed 0-10 NPRS was 0 (interquartile range -0.4 to 0.2), meaning that there was no substantial systematic change in value after the transformation algorithm was applied. The Spearman correlation coefficient between the transformed 0-10 NPRS value and the observed EQ-5D-3L pain score was 0.49. This was only slightly lower than the correlation between the EQ-5D-3L pain score and the untransformed 0-10

NPRS, at 0.50, demonstrating that the strength of the relationship between the pain measures was unchanged by transformation, which provided further reassurance that the transformation was valid in this population.

A second study used the EQ-5D-5L and the 0-10 NPRS. The transformed values from both EQ-5D-5L and pain as measured by the 0-10 NPRS, were compared when measured on the same day, (n=1956). The median difference between the original EQ-5D-5L and the 0-10 NPRS transformed to fit the range of the EQ-5D-5L was 0, with an interquartile range of -1 to 0, and a Spearman correlation coefficient of 0.31. The correlation coefficient between the untransformed values of both measures was also 0.31.

Participant Characteristics

In our sample, 10,002 participants had at least one pain assessment after stroke. The median age was 70 (interquartile range: IQR [59, 77.1], Table 1), 5,560 (55.6%) were male, a majority had a confirmed ischaemic stroke (5,421; 54.2%) and the median time since stroke was 1.4 days (IQR [1,7]). Upper-limb pain was assessed for 1,102 participants; 8 studies used the EQ-5D or the SF36, with no indication of pain localisation; further, pre-stroke pain was available for only 330 participants, of whom, 306/330 (92.8%) reported no pre-stroke pain.

Pain Assessments

For the EQ-5D-3L, 5,167/10,834 measurements were reported by the participants themselves, and the remaining by proxy. The median pain score (across all time points) when reported by the participant was 1 (IQR 1-2) compared to a median of 2 when reported by proxy (IQR 1-2). There was a significant difference between proxy and participant reported pain values ($p<0.001$). Table S1 describes the availability of pain measurements across different time points.

Prevalence and Trajectory of Post-Stroke Pain

Figure 1 describes the transformed pain scores compared to scores from each assessment tool (up to 2 years post-stroke). Reported pain generally appeared to peak in the first 100 days after stroke.

Table 2 describes the number of participants with at least one measurement of pain greater than each scale's minimum at each timepoint, defined as "some" pain. For those in whom assessment of pain was available, between 51.3% reported presence of "some" pain between 5 weeks and 3 months post-onset of stroke. For the three time periods between 4 months and 2 years post-stroke, between 62.5-67.3% of participants reported presence of "some" pain. In participants with data more than 2 years after stroke, 89.0% reported having "some" pain on at least one measurement timepoint.

Table 2 also describes the proportion of participants who had extreme pain at each time point. For those in whom assessment of pain was reported, between 3.0-5.4% reported extreme pain between onset and up to 3 months after stroke. Where assessed, between 6.1%-9.4% reported extreme pain between 4 months and 2 years after stroke. In participants with data more than 2 years after stroke, 9.5% reported having extreme pain at least once.

There were 1156 participants across four studies who had multiple pain measurements within the first year of stroke onset, however the trajectory of pain for these participants varied between studies (Figure 2). Study participant characteristics, recruitment setting, and eligibility criteria appeared to play a role in the trajectory of pain.

Participants Characteristics with and without Pain

Participants with extreme pain between 5 weeks and 3 months had worse initial stroke severity (baseline NIHSS= 15[IQR10,19] compared with 11 [8,15]; Table 3) and participants with extreme pain beyond 5 weeks post-stroke had consistently poorer independence (at the respective time points) compared to those with no or moderate pain.

Factors Associated with Pain

In studies that took place in an acute setting, poorer independence (at the respective time point) was consistently associated with presence of moderate or extreme pain at each time point (Table S2). We observed fewer reports of moderate or extreme pain in people with aphasia in the acute setting after accounting for initial stroke severity ($p<0.001$; OR=0.77, 95% CI [0.67,0.88]), and

greater reports of pain in this population after 6 months post-stroke (p=0.029; OR=2.02 95% CI [1.08,3.8]).

Poorer independence was only significantly associated with presence of extreme pain in the time period of 5 weeks to 3 months (p<0.001; OR=1.8; 95%CI [0.43,0.8]; Table 4).

In our adjusted linear regression examining reported pain severity (Table S3), poorer independence was associated with an increased pain severity across all time points in studies taking place in an acute setting; analysis of non-acute studies did not show significant relationships.

Associations between Pain, Anxiety/Depression and Vitality

Table S4 shows the adjusted linear regressions examining associations between pain and the anxiety/depression domain of the EQ-5D-3L and 5L at all available time points. Higher anxiety/ depression domain scores were significantly associated with more severe pain for both scales across all available time points.

For 621 participants, concurrent measurement of pain and vitality were available as measured by the SF-36 at a single timepoint of 90 days. Vitality scores were generated using SF-36 scoring guidelines for the domain Energy/Fatigue (vitality) and involved transposing scores to fit a scale of 0-100, where a low score indicates lower vitality[30]. Those with lower vitality reported more severe pain (Spearman Correlation coefficient=-0.32, p<0.001, Figure S2).

Discussion

We observed that targeted measurement of pain was uncommon in stroke studies, where the aims seldom related to pain outcome assessment. Only 10 from 94 identified studies included an assessment of pain, and of these, 8 were multidomain scores that included a pain item. By 2 years post-stroke, almost 10% of participants reported extreme pain; participants with extreme pain had poorer independence at each follow up time point compared to those with no or moderate pain. Presence of anxiety/depression and lower vitality were associated with more severe pain. We observed peaks of extreme pain between 4 to 6 months and beyond 2 years post-stroke. This is

consistent with previous reports of development of CPSP by 6 months of stroke onset[31]. Other reports suggest that almost a third of people have moderate to severe pain at 4 months post-stroke and this decreases to 21% by 16 months[32].

Our study expands on previous work by using a much larger sample size (n=5,094 pain assessments by 3 months, n=4,776 pain assessments between 6-12 months, n=773 with pain assessments between 1-2 years, compared to n=318 at 4 months and n=300 at 16 months in previous work [32]). Our observations are much more conservative, estimating extreme pain to affect a maximum of 9.5% beyond 2 years post-stroke. However, when using a measure of "some" pain, we observed ranges between 47.4% (at 0-4 weeks) to 89% (beyond 2 years post-stroke). We were also able to describe reporting of pain in the aphasia population, which is typically under-represented in clinical research. We observed that in the acute phase, there were fewer reports of moderate or extreme pain in those with aphasia and this was independent of initial stroke severity. By 6 months post stroke, people with aphasia reported increased prevalence of moderate or extreme pain, compared to those without aphasia.

Our findings are congruent with previous studies that reported associations between dependence, limitations in mobility, presence of depression[33] and pain[19], establishing the relationships between pain, dependency, vitality and anxiety/depression in a much larger sample size, and including both acute and non-acute recruitment settings, thereby increasing generalisability of results. While some previous studies have found a link between age and initial stroke severity with pain [34], others reported no association with age, sex, type of stroke or comorbidities[12]. Our study did not demonstrate a consistent trend of association across all time periods under investigation. Similarly, we observed inconsistent associations between sex and presence and amount of pain, whereas previous studies reported associations between female sex and risk of development of post-stroke pain[1]. However, previous observations could be due to use of single time points for assessment across those studies.

Half of stroke survivors report fatigue as a central issue after their strokes, affecting rehabilitation and ability to regain independence[35]. We reported a moderate association between vitality and pain, consistent with previous reports of an independent association between pain, fatigue[18] and depression[17].

Our study has several strengths. Data were derived from studies across a range of settings, allowing for examination of stroke in acute as well as non-acute settings and across a range of time points. Follow up of participants in stroke research for more than 2 years is uncommon yet our study included participants who were more than 2 years post-stroke. We also had data available on our anchor measure (EQ-5D-3L) in conjunction with a specific pain assessment tool (0-10 NPRS), which allowed us to explore the transformation algorithm in the context of post-stroke pain. This transformation also allowed us to make use of all available data, regardless of the assessment tool that was used in each study, thereby increasing our sample size and aggregating data across time points and settings.

Localisation of pain was available for 1,102 participants (11%); data were not available on the initiation or contents of rehabilitation in response to observed pain. Previous literature has estimated the prevalence of new post-stroke pain to be between 10%[36] to 21.8%[37], and post-stroke pain is more common in those with pre-stroke pain[38]. Data were only available on pre-stroke pain for 330 participants. We were therefore unable to identify whether our observed pain values were new or due to pre-existing pain. However, from the small sample in whom pre-stroke pain was assessed, more than 92% had no pre-stroke pain.

Post-stroke pain commonly comprises two main types: peripheral pain such as headaches, spasticity-related pain, or musculoskeletal pain; or CPSP[39], with CPSP being a commonly reported complication of strokes affecting the thalamus[40], medulla[41] and affecting 41% between 1 month and 1-year post-stroke, decreasing to 5% beyond 1-year post-stroke[42]. CPSP is associated with younger

age, smoking history, poorer initial stroke severity, and a history of depression[36]. We observed similar associations between poorer initial stroke severity, depression and presence of pain in our sample.

Our study did not differentiate by the types of pain experienced, though 4 studies included presence of limb impairment or weakness as an eligibility criterion. We were therefore unable to account for the types of pain that emerged at different time periods. We were also limited by the types of pain assessment that were used across studies in VISTA. However, it provided an indication of the types of pain assessment captured in typical stroke studies.

Conclusion

Our findings are congruent with previous recommendations in the context of CPSP[42], that clinicians should continue to check for presence of post-stroke pain up to 12 months post-stroke. Our findings also highlight the complexity of the relationships between different participant factors and pain, over different time periods. Future investigation could determine whether and when interventions may reduce the occurrence and severity of post-stroke pain, while documenting the presence of pre-stroke pain, stroke location, and type of pain.

***Appendix:**

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Supplemental Material

Figure S1: STROBE Flowchart

Figure S2: Boxplots of SF-36 Vitality Score by SF-36 Pain Score

Table S1: Availability of pain measurements by time period and scale

Table S2: Adjusted Logistic Regression: Presence of moderate or extreme pain, stratified by timepoints

Table S3: Adjusted Linear Regression: Severity of pain, stratified by timepoints

Table S4: Linear Regression for associations between severity of pain (on EQ5D 3-level and 5-level) adjusted for EQ-5D domains

Figure Titles:

Figure 1: Smoothed estimates of standardised pain scores compared to each pain assessment tool score (up to 2 years post-stroke)

Figure 2: Loess smoothed estimates of pain over time in studies with multiple measurements per person

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Tables

Table 1: Baseline characteristics

Variable		Value (N=10,002)
Age (median [IQR] years)		70.0 (59.0 – 77.1)
Sex (n male; %)		5560 (55.6%)
Time since stroke; days (median [IQR])		1.4 (1 – 7)
Stroke Type		
	Missing	3912 (39.1%)
	Assumed Ischaemic	30 (0.3%)
	Intracerebral Haemorrhage (ICH)	625 (6.2%)
	Ischaemic & ICH	4 (<0.1%)
	Confirmed Ischaemic	5421 (54.2%)
	Subarachnoid Haemorrhage (SAH)	10 (0.1%)
Baseline National Institutes of Health Stroke Scale Score (NIHSS; median [IQR])		10 (7 – 15)
Immobility at any time point (n yes; %)		1707 (17.1%)
Diabetes (n yes; %)		1355 (20.5%)
Aphasia at Baseline (n yes; %)		2269 (37.4%)

Notes: NIHSS n available=5587, diabetes n=6621, and aphasia n=6066.

Table 2: Proportion of participants with some and extreme pain at each time point

	Timepoint	**EQ5D-3L**	EQ5D-5L	0-10 Numeric Pain scale	SF-36	Transformed Pain Scale
		n with 1+ measurement of pain > scale minimum / N with 1+ measurement of pain [Binomial Proportion 95% Cis]				
Some Pain	0-4 WEEKS	26/68 (38.2%) [26.7 – 50.8%]	32/64 (50.0%) [37.2 – 62.8%]	13/63 (20.6%) [11.5 – 32.7%]	NA	63/132 (47.7%) [39.0 – 56.6%]
	5 WEEKS – 3 MONTHS	2181/4375 (49.9%) [48.4 – 51.3%]	67/96 (69.8%) [59.6 – 78.7%]	97/142 (68.3%) [60.0 – 75.9%]	354/623 (56.8%) [52.8 – 60.8%]	2615/5094 (51.3%) [50.0 – 52.7%]
	4-6 MONTHS	316/560 (56.4%) [52.2 – 60.6%]	222/292 (76.0%) [70.7 – 80.8%]	284/391 (72.6%) [67.9 – 77.0%]	NA	582/865 (67.3%) [64.0% - 70.4%]
	6 – 12 MONTHS	2597/4311 (60.2%) [58.8 – 61.7%]	329/441 (74.6%) [70.3 – 78.6%]	358/566 (63.3%) [59.1 – 67.2%]	NA	2984/4776 (62.5%) [61.1 – 63.9%]
	1 – 2 YEARS	249/461 (54.0%) [49.3 – 58.6%]	210/281 (74.7%) [69.2 – 79.7%]	220/411 (53.5%) [48.6 – 58.4%]	NA	495/773 (64.0%) [60.5 – 67.4%]
	>2 YEARS	117/141 (83.0%) [75.7 – 88.8%]	154/184 (83.7%) [77.5 – 88.7%]	198/327 (60.6%) [55.0 – 65.9%]	NA	292/328 (89.0%) [85.1 – 92.2%]
Extreme Pain	0-4 WEEKS	2/68 (2.9%) [0.4 – 10.2%]	0/64 (0%) [0.0 – 5.6%]	2/63 (3.2%) [0.4 – 11.0%]	NA	4/132 (3.0%) [0.8 – 7.6%]
	5 WEEKS – 3 MONTHS	257/4375 (5.9%) [5.2 – 6.6%]	1/96 (1.0%) [0.0 – 5.7%]	8/142 (5.6%) [2.5 – 10.8%]	11/623 (1.8%) [0.9- 3.1%]	274/5094 (5.4%) [4.8 – 6.0%]
	4-6 MONTHS	52/560 (9.3%) [7.0 – 12.0%]	5/292 (1.7%) [0.6 – 4.0%]	28/391 (7.2%) [4.8 – 10.2%]	NA	81/865 (9.4%) [7.5 – 11.5%]

	6 – 12 MONTHS	260/4311 (6.0%) [5.3 – 6.8%]	8/441 (1.8%) [0.8 - 3.5%]	31/566 (5.5%) [3.8 - 7.7%]	NA	292/4776 (6.1%) [5.5 – 6.8%]
	1 – 2 YEARS	31/461 (6.7%) [4.6 -9.4%]	11/281 (3.9%) [2.0 - 6.9%]	13/411 (3.2%) [1.7- 5.3%]	NA	53/773 (6.9%) [5.2 – 8.9%]
	>2 YEARS	19/141 (13.5%) [8.3- 20.2%]	6/184 (3.3%) [1.2 – 7.0%]	9/327 (2.8%) [1.3 -5.2%]	NA	31/328 (9.5%) [6.5 -13.1%]

Table 3: Unadjusted associations between the presence of extreme pain and participant characteristics

Time Period	Variable	Extreme Pain	No, or moderate, Pain	Mann Whitney / $\chi 2$ p-value: Pain vs. No Pain
		Median / N (IQR / %)		
0-4 weeks (n=132, studies=2)	Age	66 (58 – 73)	69 (55 – 80)	0.868
	Male Sex	1 (25.0%)	75 (58.6%)	0.409
	Initial Stroke Severity	Insufficient data		
	Presence of Baseline Severe-Global Aphasia	0	10 (8.6%)	1.000
	Diabetes	No data		
	Independence	3.5 (3.25- 3.75)	4 (4 – 5)	0.200
	Mobility	2.5 (1.75 – 3)	1.5 (1 – 2)	0.220
5 weeks – 3 months (n=5094, Studies=7)	Age	69 (58 - 77)	68 (58 - 76)	0.396
	Male Sex	**124 (45.3%)**	**2719 (56.4%)**	**<0.001**
	Initial Stroke Severity	**15 (10 – 19)**	**11 (8 – 15)**	**<0.001**
	Presence of Baseline Severe-Global Aphasia	100 (37.2%)	1895 (39.5%)	0.483
	Diabetes	53 (23.0%)	920 (21.5%)	0.632
	Independence	**4 (3 – 5)**	**2 (1 – 4)**	**<0.001**
	Mobility	**2 (1 – 3)**	**3 (2 – 3)**	**<0.001**
4 months – 6 months (n=865, studies=7)	Age	64 (51- 72)	62 (52- 71)	0.593
	Male Sex	44 (54.3%)	473 (60.3%)	0.352
	Initial Stroke Severity	6 (4 – 20.5)	8 (4 – 18)	0.899
	Presence of Baseline Severe-Global Aphasia	23 (35.9%)	281 (40.5%)	0.563
	Diabetes	6 (18.2%)	10 (9.7%)	0.315
	Independence	**4 (3 – 5)**	**3 (2 – 4)**	**0.013**
	Mobility	3 (1 – 3)	3 (2 – 3)	0.156
> 6 months (n=5229, studies=6)	Age	68 (60- 78)	70 (59 – 78)	0.205
	Male Sex	196 (54.7%)	2709 (55.6%)	0.792
	Initial Stroke Severity	6 (3 – 13)	6 (4 – 11)	0.979
	Presence of Baseline Severe-Global Aphasia	48 (36.6%)	433 (34.8%)	0.742
	Diabetes	25 (16.4%)	354 (18.2%)	0.656
	Independence	**4 (3 – 5)**	**3 (2 – 4)**	**<0.001**
	Mobility	**3 (1.13 – 3)**	**3 (3 – 3)**	**<0.001**

Table 4: Adjusted Logistic Regression: Presence of "extreme" pain, stratified by timepoints

Time Period	Covariate	Value	Acute Studies			Non-Acute Studies		
			Adjusted Odds Ratio Estimates					
			Point Estimate	95% Wald Confidence Limits	P-value	Point Estimate	95% Wald Confidence Limits	P-value
5 weeks -3 months (4 Acute studies: n=4803, 3 chronic/mixed studies: n = 134)	Age		0.983	(0.972, 0.994)	0.003	0.993	(0.929, 1.061)	0.836
	Male Sex		0.671	(0.513, 0.878)	0.004	2.797	(0.280, 27.900)	0.381
	Higher Initial Stroke Severity		1.033	(1.007, 1.060)	0.013	1.141	(0.964, 1.350)	0.125
	Mobility Problems		1.175	(0.802, 1.722)	0.408	0.559	(0.075, 4.163)	0.570
	Diabetes	No	{ref}			Omitted: 82% missing		
		Yes	0.983	(0.706, 1.368)	0.917			
		Missing	0.492	(0.297, 0.816)	0.006			
	Presence of Aphasia at Baseline		0.583	(0.425, 0.800)	0.001	0.983	(0.092, 10.503)	0.989
	Poorer Independence		1.823	(1.559, 2.132)	<0.001	Omitted: 80% missing		
4 months – 6 months (1 Acute study: n=343, 6 chronic/mixed studies: n = 271)	Age		0.917	(0.868, 0.968)	0.002	0.938	(0.953, 1.013)	0.263
	Male Sex		0.597	(0.198, 1.799)	0.359	0.804	(0.333, 1.944)	0.628
	Higher Initial Stroke Severity		1.039	(0.980, 1.102)	0.195	0.989	(0.843, 1.160)	0.893
	Mobility Problems		1.630	(0.331, 8.023)	0.548	1.052	(0.405, 2.734)	0.917
	Diabetes		Omitted as 100% missing			Omitted: 72% missing		
	Presence of Aphasia at Baseline		1.459	(0.244, 8.735)	0.679	0.811	(0.214, 3.078)	0.758
	Poorer Independence		1.390	(0.708, 2.731)	0.339	Omitted: 84% missing		
> 6 months (1 Acute study: n=338, 5 chronic/mixed studies: n = 660)	Age		0.958	(0.919, 0.999)	0.044	0.984	(0.963, 1.006)	0.163
	Male Sex		1.267	(0.539, 2.981)	0.587	1.165	(0.625, 2.173)	0.631
	Higher Initial Stroke Severity		0.967	(0.919, 1.016)	0.183	0.921	(0.812, 1.045)	0.203
	Mobility Problems		1.187	(0.334, 4.219)	0.791	2.774	(1.441, 5.341)	0.002
	Diabetes		Omitted as 100% missing			Omitted: 82% missing		
	Presence of Aphasia at Baseline		1.172	(0.389, 3.531)	0.779	1.531	(0.725, 3.232)	0.264
	Poorer Independence		1.720	(0.996, 2.971)	0.052	Omitted: 80% missing		