Tissue-Engineered Scaffolds for Spinal Cord Regeneration: A Systematic Review of Preclinical Animal Studies

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1 Introduction

Spinal cord injury (SCI) is a major cause of persistent neurological disability, with damage to the spinal cord producing impairments in motor, sensory and autonomic function that can affect long-term independence and quality of life[1,2]. SCI also produces a prolonged secondary injury response involving inflammation, vascular dysfunction, demyelination, and cell death. Although acute clinical management and rehabilitation can limit secondary complications and maximise preservation of residual function, there is currently no treatment capable of reliably restoring the complex neural circuitry lost following established [3].

Neuronal and glial death, vascular disruption, and progressive tissue degradation can culminate in the formation of a cystic cavity at the lesion epicentre, surrounded by reactive astrocytes, microglia, macrophages, fibroblast-like cells and altered extracellular matrix[4,5]. The resulting environment is the primary problem for regenerative medicine: the tissue that must be repaired has simultaneously lost its native architecture and acquired molecular signals that discourage extensive neural regrowth.

Reactive gliosis is an example of this problem. Astrocytes proliferate and become reactive around the lesion, contributing to formation of the glial scar that restricts the spread of inflammation and helps contain secondary damage during the acute response[5,6]. As the scar matures, however, its extracellular matrix becomes enriched in inhibitory molecules, particularly chondroitin sulphate proteoglycans (CSPGs), which can interfere with axonal extension and sprouting[4,6]. The damaged spinal cord develops an environment that is simultaneously protective and inhibitory: the scar can limit the expansion of injury while subsequently restricting the very axonal growth required for reconstruction[5]. Axonal regeneration is further restricted by inhibitory signals associated with damaged myelin and the extracellular matrix. Molecules including Nogo-A, myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein can activate intracellular pathways that suppress axonal growth, while CSPGs within the glial scar and perineuronal environment interfere with extension at the neuronal growth cone[4,7].

These barriers provide the biological basis for tissue-engineering approaches to SCI. Rather than relying exclusively on endogenous repair, tissue engineering seeks to replace or supplement components of the damaged neural environment using combinations of biomaterials, cells, and biological signals[3]. Within this field, scaffolds are particularly attractive because they can occupy the lesion cavity, provide a three-dimensional substrate for cellular attachment and potentially establish a physical bridge between regions of surviving spinal cord[8].

Scaffold materials can be engineered to modify these cues through differences in composition, surface chemistry, stiffness, porosity, degradation rate, and three-dimensional architecture[3,9]. Scaffold architecture is particularly relevant because neural tissue is highly organised. Interconnected pores can facilitate cellular infiltration and transport of nutrients and waste products, while channels, aligned fibres and other anisotropic structures can provide directional guidance for axonal growth[12]. The geometry, orientation and internal organisation of a scaffold may influence regeneration independently of its chemical composition.

Scaffolds may also modify the biological environment directly. Biomaterial scaffolds have been investigated for their capacity to reduce apoptosis, inflammation and scar formation while promoting angiogenesis, neurogenesis, and axonal growth[8]. The scaffold can therefore function as both a physical matrix and a local therapeutic platform. This has encouraged the development of combination scaffold interventions in which the biomaterial is integrated with additional therapeutic components. Cells may be incorporated to provide trophic support, replace, or supplement damaged cell populations, or contribute to remodelling of the injured environment, while the scaffold provides protection, retention, and physical guidance[10]. Similarly, growth factors and pharmacological agents can be incorporated into scaffolds to provide localised or sustained delivery at the lesion[3,8]. The tissue-engineering triad of cells, biomaterial and environmental factors therefore provides a means of addressing several components of SCI pathology within a single intervention[3].

The inclusion of additional therapeutic components is particularly relevant when defining scaffold-based interventions for evidence synthesis. A cell-containing scaffold differs fundamentally from administration of the same cells without a biomaterial because the scaffold can alter cell localisation, retention, survival, differentiation, and interaction with host tissue[10]. Similarly, a drug or growth factor incorporated into a scaffold is not necessarily biologically equivalent to the same agent administered independently because the biomaterial can alter its spatial distribution and release[8]. Recent systematic evidence reflects this distinction, with bioengineered scaffold research encompassing scaffolds used both independently and in combination with bioactive agents, pharmacological treatments, and cellular transplants[11]. Scaffold-only interventions and scaffold-plus-therapy interventions can therefore be examined within a scaffold-based evidence base when the scaffold forms an integral part of treatment, whereas interventions in which no scaffold is present represent a different therapeutic strategy.

The preclinical evidence is further complicated by substantial heterogeneity in the animal models used to investigate scaffold-based interventions. A systematic evaluation of biomaterial SCI research identified 404 individual experiments representing 149 unique animal models, with variation in species, strain, sex, injury level, and injury method[12]. A multidomain assessment is especially important because recovery after SCI can occur through several mechanisms. Surviving axons may undergo plasticity or sprouting, spared pathways may compensate for damaged circuitry, oligodendrocyte precursor cells may contribute to remyelination, and transplanted or endogenous cells may alter the local environment without necessarily reconstructing the original neural architecture[5,13]. Behavioural improvement can therefore occur without complete anatomical regeneration, while histological evidence of axonal growth does not by

itself demonstrate that newly formed connections are physiologically effective[5]. Examining behavioural, histological, molecular, and electrophysiological domains separately can therefore distinguish different manifestations of recovery rather than treating all positive findings as equivalent evidence of regeneration.

The central difficulty is therefore not a lack of promising interventions, but the difficulty of determining what constitutes successful regeneration and which characteristics of scaffold-based treatment are associated with it. A scaffold may reduce lesion volume without producing substantial behavioural recovery; another may promote axonal growth while having little demonstrable electrophysiological effect; a third may produce behavioural improvement through preservation or plasticity of spared circuitry rather than regeneration through the lesion itself[4,5]. These possibilities make it problematic to rely on a single outcome measure when evaluating the regenerative capacity of scaffold-based therapies. A synthesis that considers multiple biological and functional domains can instead distinguish between preservation, structural regeneration, physiological recovery, and behavioural improvement.

The expanding preclinical literature provides both an opportunity and a methodological challenge for evaluating scaffold-based approaches to SCI. Scaffold-based tissue engineering can simultaneously address tissue loss, provide physical guidance, alter the extracellular environment and deliver additional regenerative components, making it one of the more versatile approaches investigated for SCI repair[3,8]. At the same time, the breadth of scaffold compositions, architectures and combination therapies means that interventions sharing the same broad classification may have different mechanisms and biological effects[9,11]. Differences in animal models and methodological quality further complicate comparisons, while the use of behavioural, histological, molecular, and electrophysiological measures captures different dimensions of recovery rather than a single uniform endpoint[4,12]. A rigorous synthesis must therefore preserve these distinctions rather than flattening the evidence into a simple comparison of whether an intervention "worked."

1.1 Rationale and Objectives

This systematic review therefore synthesises preclinical evidence on scaffold-based tissue-engineering interventions for SCI, examining scaffold characteristics in relation to behavioural, histological, molecular, and electrophysiological outcomes. Methodological quality and translational potential are also assessed to evaluate the reliability and clinical relevance of reported effects and to explore whether scaffold characteristics are associated with differences in regenerative outcomes.

Aims

To evaluate the effectiveness of tissue-engineered scaffolds for spinal cord regeneration in preclinical animal models by synthesising behavioural, histological, molecular, and electrophysiological outcomes.

Objectives

Primary Objectives

1. To classify and characterise the scaffold materials, architectures, fabrication methods, and therapeutic strategies investigated for SCI repair.
2. To evaluate the regenerative effects of scaffold-based interventions across behavioural, histological, molecular, and electrophysiological domains, and to calculate predefined domain-specific and overall regeneration scores.

Secondary Objectives

3. To assess methodological quality and risk of bias among included studies.
4. To evaluate the translational potential of scaffold-based interventions and identify factors relevant to future clinical development.

2 Methodology

2.1 Study Design

A systematic review was conducted to evaluate scaffold-based tissue-engineering interventions for SCI in preclinical animal models. The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[14]. The research question and eligibility criteria were predefined using the Population, Intervention, Comparator and Outcomes (PICO) framework.

The population comprised only animal-models with experimentally induced SCI. Eligible interventions were tissue-engineered biomaterial scaffolds used either independently or in combination with additional therapeutic components, including cells, growth factors, drugs etc, provided that a scaffold formed a large component. Cell, drug, or growth-factor-only interventions were excluded. Comparators included untreated SCI, sham, vehicle, or standard-treatment controls. Outcomes comprised behavioural recovery, histological and molecular evidence of regeneration, electrophysiological recovery, and safety-related measures.

A predefined review protocol and methodology were established before screening and data extraction. However, owing to the time constraints of the Laidlaw Research Programme, prospective registration was not completed before screening commenced.

2.2 Search Strategy and Study Selection

MEDLINE (Ovid), Embase and Web of Science were searched from database inception to 10 July 2026. Searches combined controlled vocabulary and free-text terms relating to SCI and tissue engineering/scaffolds, with database-specific adaptations where required. Terms relating to regeneration and animal models were not mandatory search concepts to maximise sensitivity, with eligibility subsequently determined during screening. No publication-date restriction was applied, while searches were restricted to English-language publications. Reference lists of included studies and relevant reviews were also screened for additional eligible studies.

Records were imported into Zotero, where duplicates were removed before screening. Titles and abstracts were screened against predefined eligibility criteria, followed by full-text assessment of potentially eligible studies. Screening and extraction were performed by a single reviewer, with uncertainties discussed with the academic supervisor. The study selection process was documented using a PRISMA flow diagram[14].

2.3 Data Extraction and Synthesis

Data were extracted using a predefined Microsoft Excel form covering study characteristics, animal and injury models, scaffold composition and architecture, fabrication methods, material properties, additional therapeutic components, and reported outcomes.

Due to substantial heterogeneity, quantitative meta-analysis was not considered appropriate. Instead, predefined scoring systems were used to allow standardised comparison across heterogeneous outcomes. Outcomes were scored according to improvement relative to injury controls, with domain-specific scores calculated for behavioural, histological/molecular, and electrophysiological outcomes. These were combined to generate an overall regenerative capability score where sufficient data were available. Missing or unreported outcomes were excluded from scoring rather than interpreted as absence of improvement.

Scaffold characteristics were grouped using a hierarchical classification developed for the review, enabling comparison of regenerative outcomes between biomaterial classes and designs. Descriptive statistics, including mean, median, range and standard deviation, were used to summarise outcomes across scaffold categories.

2.4 Risk of Bias and Translational Assessment

Methodological quality was assessed using the SYRCLE risk-of-bias tool for animal intervention studies[15]. Risk of bias was assessed separately from regenerative outcomes and considered when interpreting evidence reliability.

Translational potential was assessed using a predefined Translational Readiness Index developed for scaffold-based SCI research. The index considered model relevance, functional evidence, safety, clinical feasibility, and external validation. Regenerative performance, methodological quality, and translational readiness were analysed independently to avoid conflating biological efficacy with evidence reliability or clinical applicability.

2.5 Full Protocol

Avaible on Request

3 Results

3.1 Study Selection

Where a publication investigated multiple eligible scaffold interventions, the publication was excluded from the present analysis rather than treating each intervention as an independent observation. This approach was adopted to maintain a single eligible intervention per included study and ensure consistent data extraction and comparison across the dataset within the available review timeframe.

A further limitation was the exclusion of publications containing multiple eligible scaffold interventions. Although this ensured a consistent single-intervention structure across the dataset, it may have excluded relevant evidence and reduced representation of studies directly comparing different scaffold strategies within the same experimental setting.

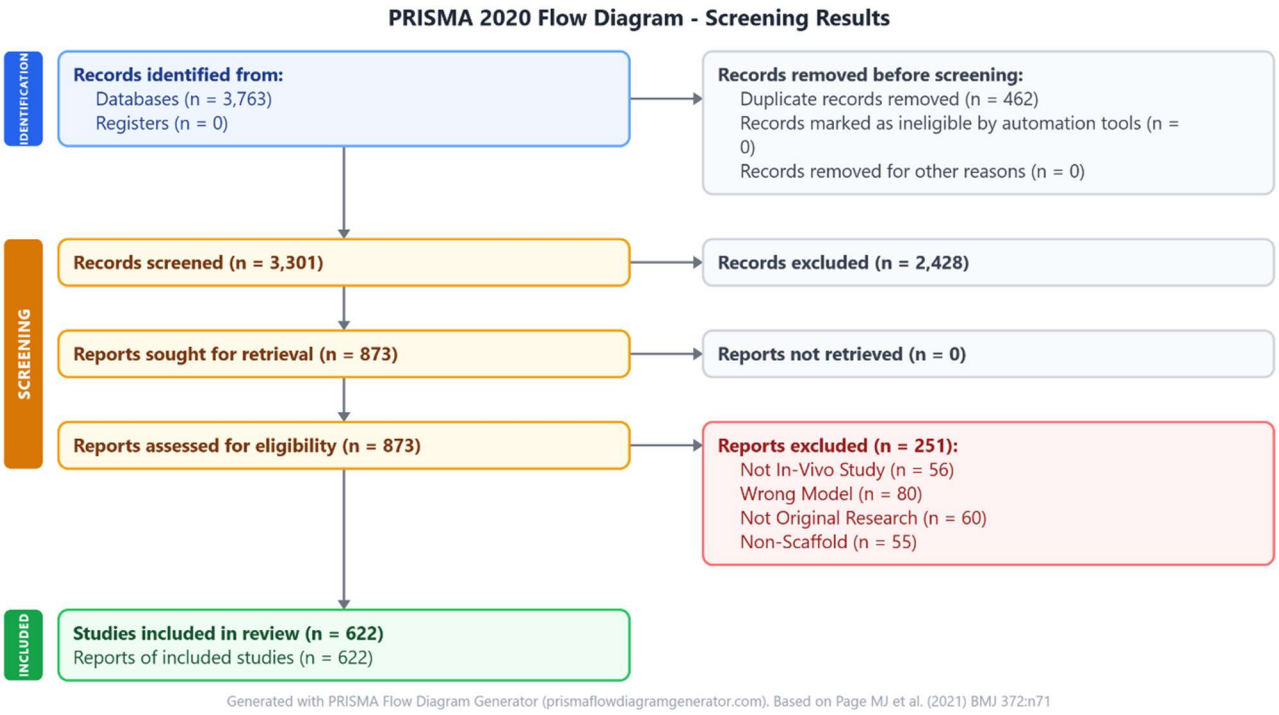

Figure 3.1 PRISMA flow diagram showing identification, screening, eligibility, assessment and inclusion of studies.

Individual Intervention Extraction:

3.2 Characteristics of Included Studies

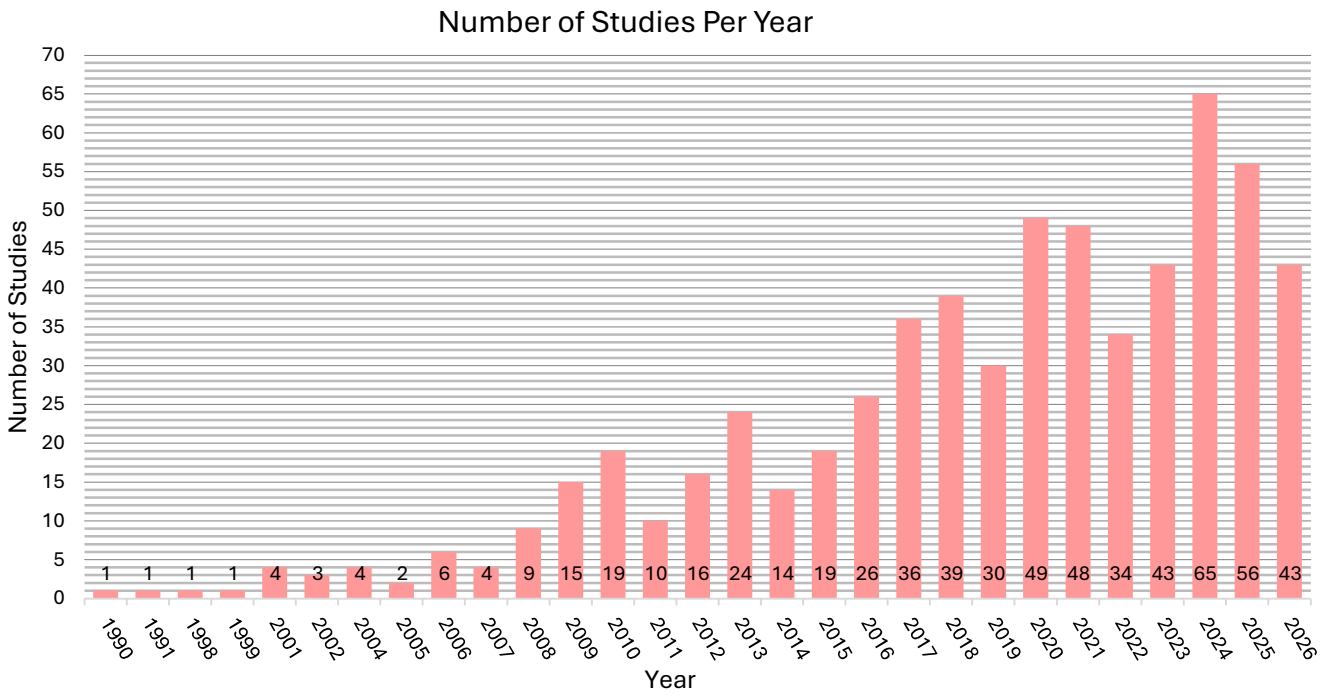

Figure 3.2. Number of studies per year. Number of included studies published in each year.

3.3 Outcome Reporting

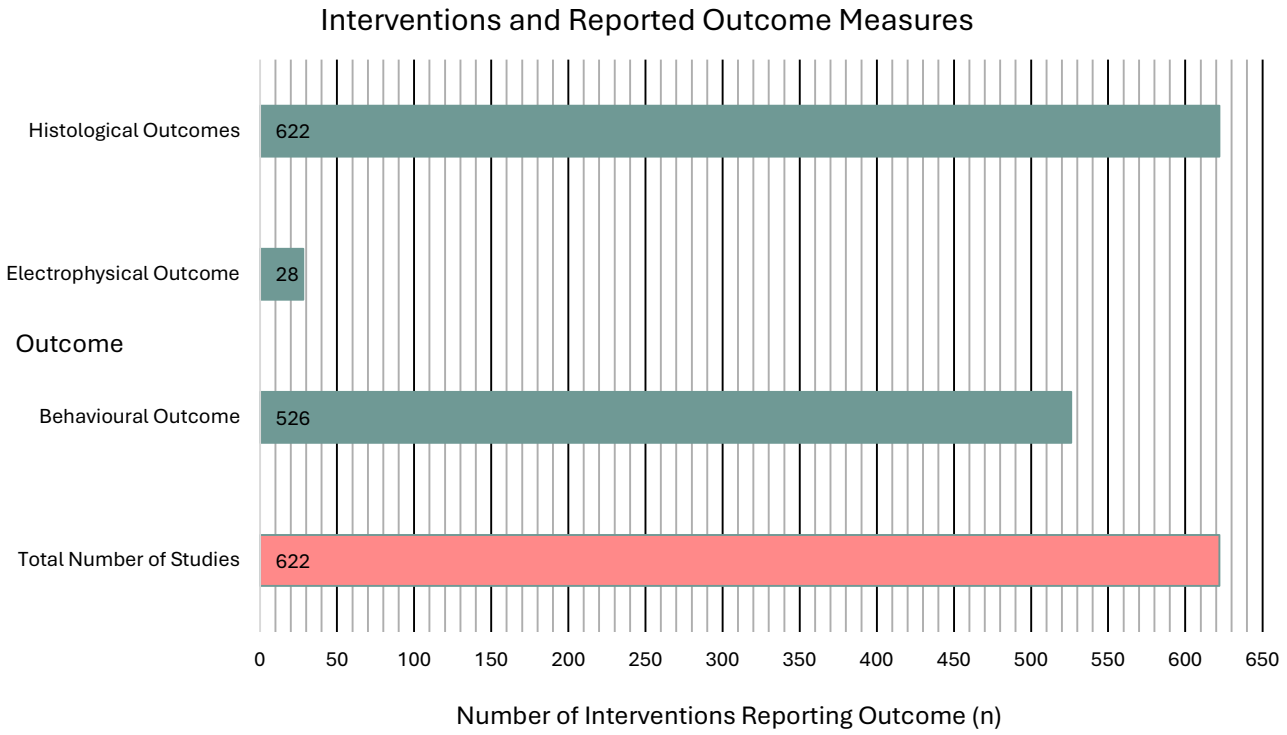

Figure 3.3.1. Number of interventions reporting outcome measures. Number of interventions reporting histological, behavioural and electrophysiological outcome measures.

Scaffold Class	Number of Interventions In Category	Number Reporting Histological Outcome	Average Number of Histological Domains Assessed	Number Reporting Behavioural Outcome	Number Reporting Electrophysical Outcome
All Interventions (Ungrouped)	622	622	5.551	526	28
Natural biomaterial	183	183	5.683	157	13
Synthetic polymer	130	130	5.677	109	3
Composite	177	177	5.542	148	6
Decellularised extracellular matrix	28	28	4.821	24	2
Electroconductive	53	53	5.491	46	1
Injectable (if not otherwise classifiable)	19	19	4.737	15	0
Metallic/mineral	2	2	5.000	2	0
Not Reported/Not Clear	30	30	5.600	25	3

Table 3.3.2. Outcome reporting by scaffold class. Number of interventions reporting each outcome measure, categorised by scaffold class.

Scaffold Material	Number of Interventions in Category	Number Reporting Histological Outcome	Average Number of Histological Domains Assessed	Number Reporting Behavioural Outcome	Number Reporting Electrophysical Outcome
Collagen	86	86	5.384	70	4
Gelatine	52	52	5.577	46	4
Chitosan	76	76	5.526	63	4
Hyaluronic acid	52	52	5.788	44	1
Alginate	30	30	5.867	27	1
Silk fibroin	30	30	5.700	27	2
Fibrin	21	21	5.762	18	1
Matrigel	6	6	5.833	6	0
Decellularised ECM	43	43	5.070	37	3
Agarose	5	5	5.400	5	0
Xanthan	1	1	4.000	0	0
Cellulose	7	7	4.571	5	0
PLGA	61	61	5.721	51	1
PLA	19	19	5.789	16	0
PCL	34	34	5.588	30	0
PEG	23	23	5.478	21	0
PGA	3	3	4.667	2	1
PVA	4	4	4.750	3	0
PU	2	2	3.000	1	0
PMMA	0	0	NR	0	0
PEGDA	8	8	6.125	6	0
Other	12	12	5.583	11	1
Not reported	69	69	5.725	59	4
All Interventions (Ungrouped)	622	622	6.383	2	28

Table 3.3.3. Outcome reporting by scaffold material. Number of interventions reporting each outcome measure, categorised by scaffold material.

Scaffold Architecture	Number of Interventions in Category	Number Reporting Histological Outcome	Average Number of Histological Domains Assessed	Number Reporting Behavioural Outcome	Number Reporting Electrophysical Outcome
Hydrogel	249	249	5.610	212	11
Sponge	35	35	5.343	30	0
Foam	7	7	5.143	6	1
Electrospun	68	68	5.485	57	2
Porous scaffold	140	140	5.379	123	4
3D printed	41	41	5.659	34	1
Tube/channel	92	92	5.707	82	4
Microspheres	21	21	5.810	16	1
Nanofiber	71	71	5.577	61	3
Aligned scaffold	73	73	5.699	61	3
Not Reported	81	81	5.457	64	4
All Interventions (Ungrouped)	622	622	6.383	2	28

Table 3.3.4. Outcome reporting by scaffold architecture. Number of interventions reporting each outcome measure, categorised by scaffold architecture.

Scaffold Combination Therapy	Number of Interventions in Category	Number Reporting Histological Outcome	Average Number of Histological Domains Assessed	Number Reporting Behavioural Outcome	Number Reporting Electrophysical Outcome
All Interventions (Ungrouped)	622	622	6.383	2	28
None	206	206	5.597	177	8
Cells	209	209	5.560	176	7
Growth Factor	81	81	5.519	66	5
Drug/Pharmaceutical	81	81	5.407	68	2
Growth Factor	30	30	5.733	25	2
Rehabilitation	6	6	5.000	5	0
Surgical Incision	1	1	5.000	1	0
Biomolecules	14	14	5.714	11	2
Other Combinations	18	18	5.667	16	0
Multiple (>3)	24	24	5.375	20	2

Table 3.3.5. Outcome reporting by combination therapy. Number of interventions reporting each outcome measure, categorised by scaffold combination therapy.

3.4 Histological Outcome Assessment

3.4.1 Frequency of Histological Domains Assessed Across Interventions

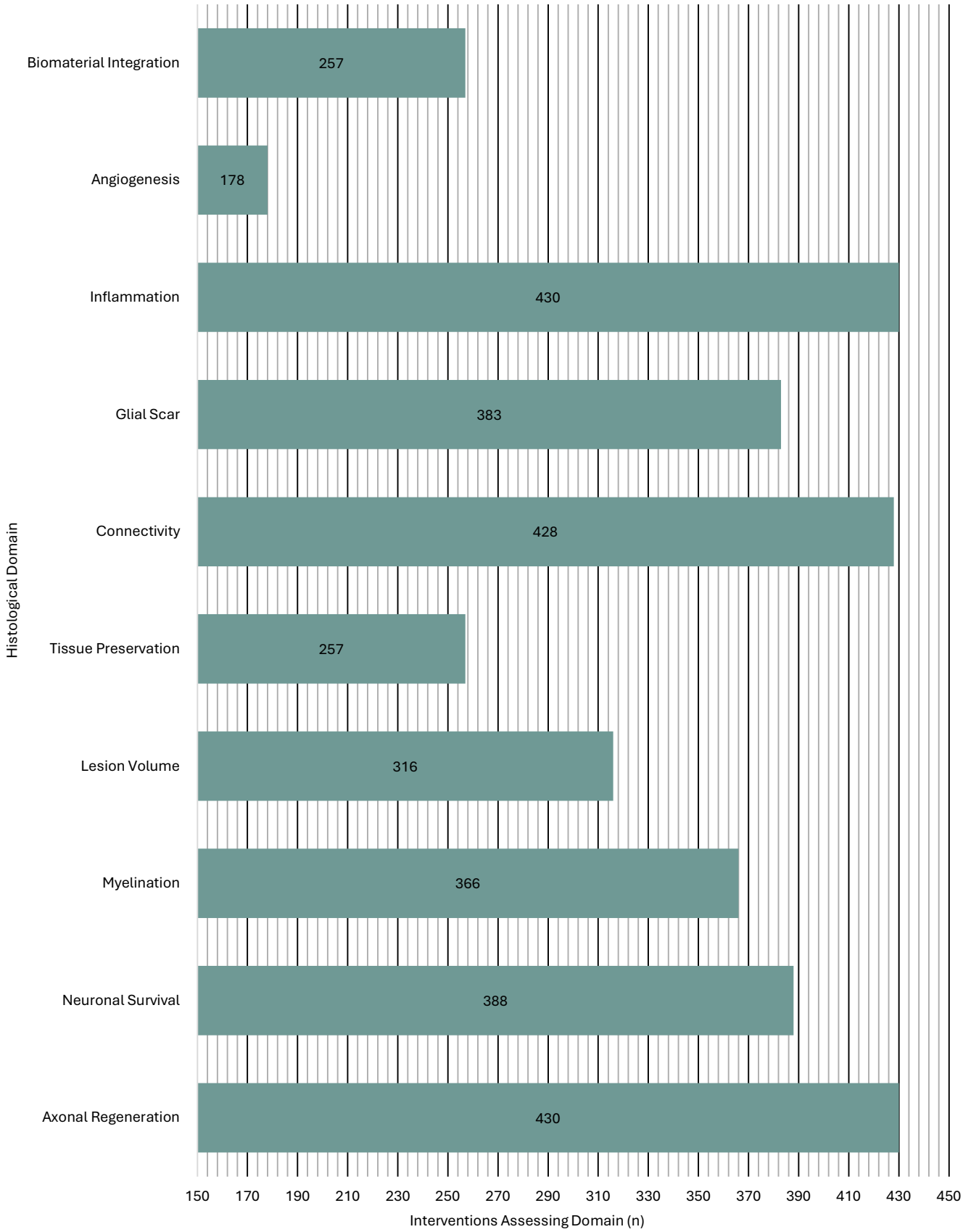

Figure 3.4.1. Frequency of histological domains assessed across interventions. Frequency with which individual histological outcome domains were assessed across included interventions.

3.4.2 Mean Scores for Histological Domains Across Interventions

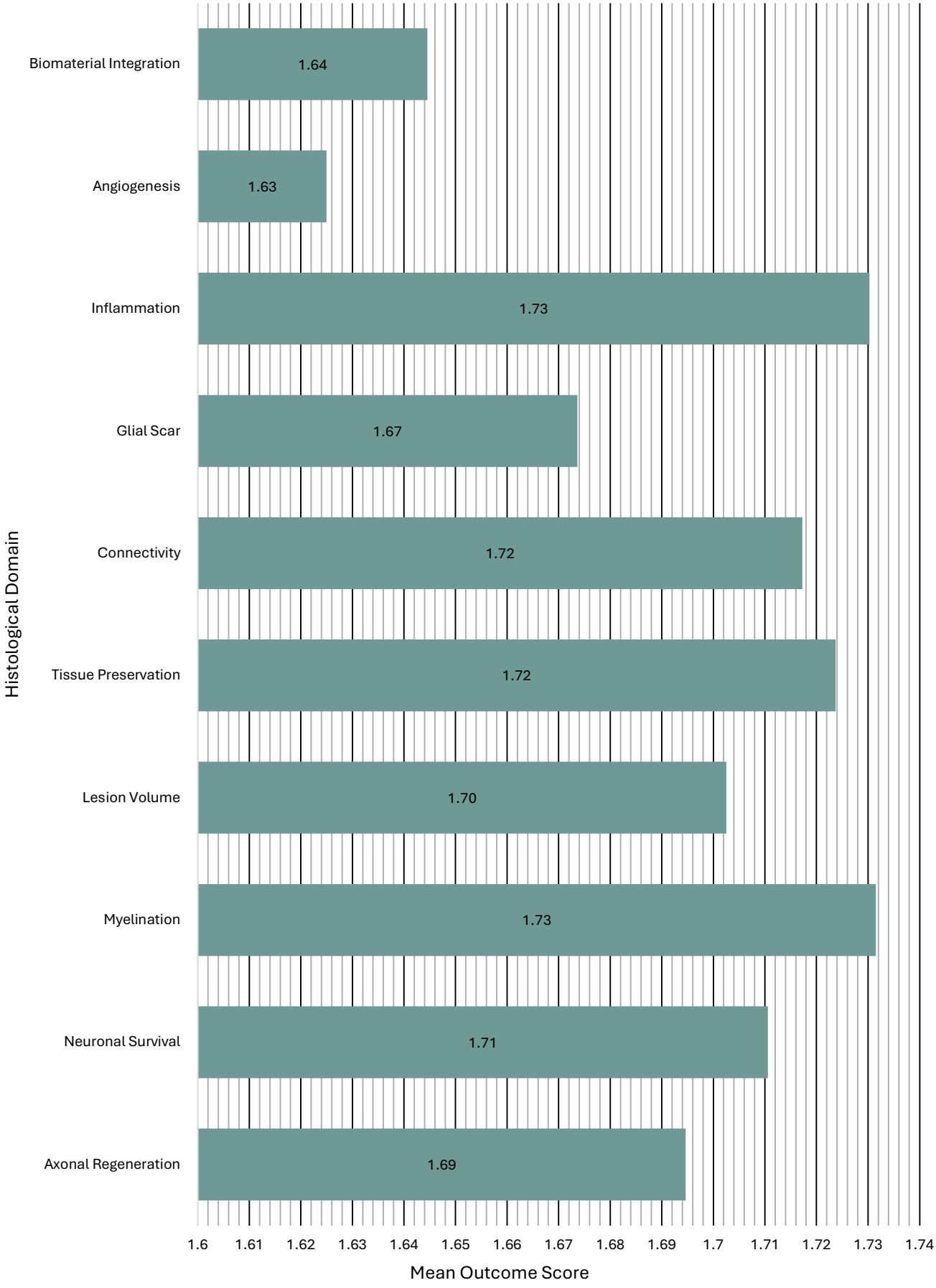

Figure 3.4.2. Mean scores for histological domains across interventions. Mean scores assigned to individual histological outcome domains across included interventions.

3.5 Risk of Bias

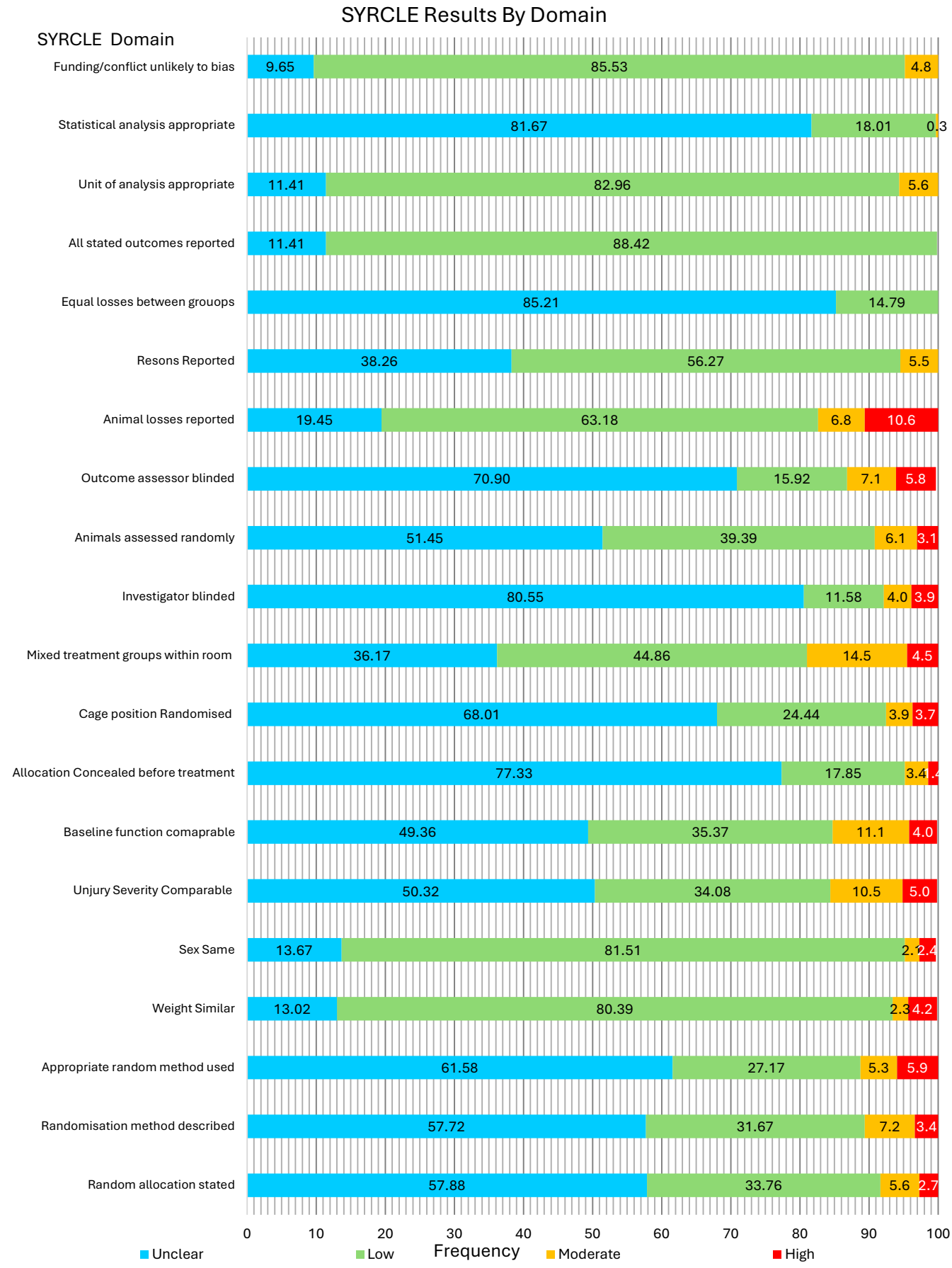

Figure 3.5. SYRCLE risk-of-bias assessment. Frequency of risk-of-bias judgements across the assessed SYRCLE domains.

3.6 Scaffold Characteristics and Regenerative Outcomes

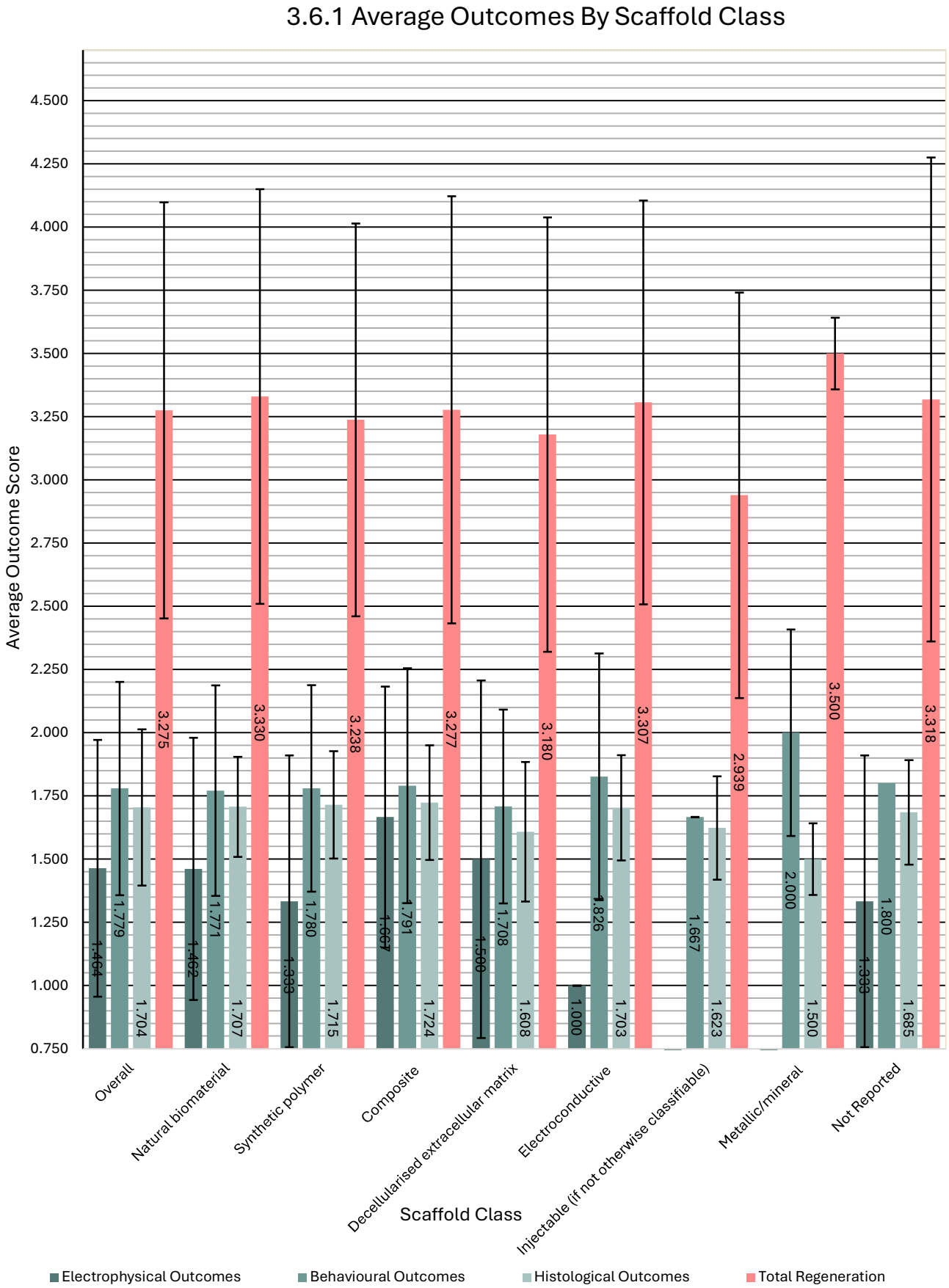

Figure 3.6.1. Average outcome by scaffold class. Mean outcome score across outcome domains for each scaffold class.

	Behavioural mean	Behavioural median	Behavioural SD	Behavioural range	Electrophysical Mean	Electrophysical Median	Electrophysical SD	Electrophysical Range	Histological mean	Histological Median	Histological SD	Histological range	Total Regeneration Average	Total Regeneration Median	Total Regeneration SD	Total Regeneration Range
Overall	1.78	2.00	0.42	1.00	1.46	1.00	0.51	1.00	1.70	1.71	0.31	1.00	3.28	3.57	0.82	5.00
Natural biomaterial	1.77	2.00	0.42	1.00	1.46	1.00	0.52	1.00	1.71	1.75	0.20	1.00	3.33	3.60	0.82	4.75
Synthetic polymer	1.78	2.00	0.42	1.00	1.33	1.00	0.58	1.00	1.71	1.71	0.21	1.00	3.24	3.57	0.78	3.30
Composite	1.79	2.00	0.41	1.00	1.67	2.00	0.52	1.00	1.72	1.75	0.23	2.00	3.28	3.60	0.84	4.60
Decellularised extracellular matrix	1.71	2.00	0.46	1.00	1.50	1.50	0.71	1.00	1.61	1.63	0.28	1.00	3.18	3.33	0.86	4.24
Electroconductive	1.83	2.00	0.38	1.00	1.00	1.00	NR	0.00	1.70	1.67	0.21	0.86	3.31	3.60	0.80	3.69
Injectable (if not otherwise classifiable)	1.67	2.00	0.49	1.00	NR	NR	NR	NR	1.62	1.67	0.20	0.67	2.94	3.33	0.80	2.47
Metallic/mineral	2.00	2.00	0.00	0.00	NR	NR	NR	NR	1.50	1.50	0.14	0.20	3.50	3.50	0.14	0.20
Not Reported	1.80	2.00	0.41	1.00	1.33	1.00	0.58	1.00	1.68	1.71	0.21	0.71	3.32	3.45	0.96	4.00

Table 3.6.2. Detailed analysis of outcomes by scaffold class. Outcome scores and descriptive statistics for each scaffold class.

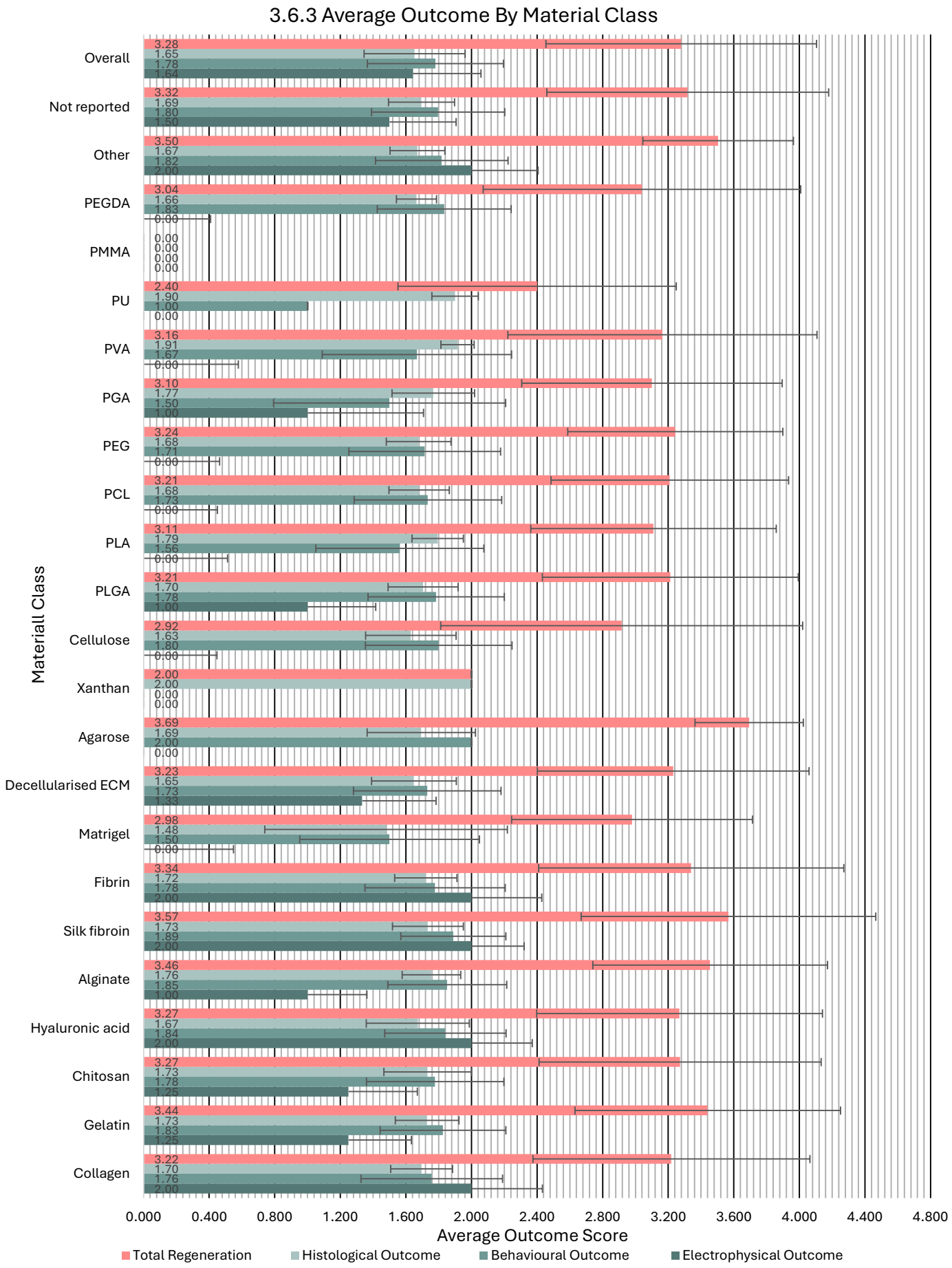

Figure 3.6.3. Average outcome by scaffold material. Mean outcome score across outcome domains for each scaffold material.

	Behavioural mean	Behavioural median	Behavioural SD	Behavioural range	Electrophysical Mean	Electrophysical Median	Electrophysical SD	Electrophysical Range	Histological mean	Histological Median	Histological SD	Histological range	Total Regeneration Average	Total Regeneration Median	Total Regeneration SD	Total Regeneration Range
Collagen	1.76	2.00	0.43	1.00	2.00	2.00	0.00	0.00	1.70	1.71	0.19	1.00	3.22	3.50	0.84	4.67
Gelatine	1.83	2.00	0.38	1.00	1.25	1.00	0.50	1.00	1.73	1.75	0.19	0.86	3.44	3.67	0.81	4.35
Chitosan	1.78	2.00	0.42	1.00	1.25	1.00	0.50	1.00	1.73	1.80	0.27	2.00	3.27	3.67	0.86	4.67
Hyaluronic acid	1.84	2.00	0.37	1.00	2.00	2.00	NR	0.00	1.67	1.71	0.31	2.00	3.27	3.60	0.87	4.21
Alginate	1.85	2.00	0.36	1.00	1.00	1.00	NR	0.00	1.76	1.71	0.18	0.63	3.46	3.67	0.72	3.22
Silk fibroin	1.89	2.00	0.32	1.00	2.00	2.00	0.00	0.00	1.73	1.78	0.22	0.83	3.57	3.75	0.90	4.21
Fibrin	1.78	2.00	0.43	1.00	2.00	2.00	NR	0.00	1.72	1.67	0.19	0.67	3.34	3.67	0.93	4.17
Matrigel	1.50	1.50	0.55	1.00	NR	NR	NR	NR	1.48	1.72	0.74	2.00	2.98	2.82	0.73	2.00
Decellularised ECM	1.73	2.00	0.45	1.00	1.33	1.00	0.58	1.00	1.65	1.67	0.26	1.00	3.23	3.40	0.83	4.17
Agarose	2.00	2.00	0.00	0.00	NR	NR	NR	NR	1.69	1.80	0.33	0.86	3.69	3.80	0.33	0.86
Xanthan	NR	NR	NR	NR	NR	NR	NR	NR	2.00	2.00	NR	0.00	2.00	2.00	NR	0.00
Cellulose	1.80	2.00	0.45	1.00	NR	NR	NR	NR	1.63	1.57	0.28	0.67	2.92	3.33	1.10	2.67
PLGA	1.78	2.00	0.42	1.00	1.00	1.00	NR	0.00	1.70	1.71	0.21	0.80	3.21	3.50	0.78	2.50
PLA	1.56	2.00	0.51	1.00	NR	NR	NR	NR	1.79	1.83	0.16	0.50	3.11	3.00	0.75	2.33
PCL	1.73	2.00	0.45	1.00	NR	NR	NR	NR	1.68	1.67	0.18	0.67	3.21	3.50	0.72	2.60
PEG	1.71	2.00	0.46	1.00	NR	NR	NR	NR	1.68	1.67	0.20	0.67	3.24	3.50	0.66	2.38
PGA	1.50	1.50	0.71	1.00	1.00	1.00	NR	0.00	1.77	1.80	0.25	0.50	3.10	2.80	0.79	1.50
PVA	1.67	2.00	0.58	1.00	NR	NR	NR	NR	1.91	1.93	0.10	0.20	3.16	3.33	0.94	2.00
PU	1.00	1.00	NR	0.00	NR	NR	NR	NR	1.90	1.90	0.14	0.20	2.40	2.40	0.85	1.20
PMMA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PEGDA	1.83	2.00	0.41	1.00	NR	NR	NR	NR	1.66	1.69	0.12	0.40	3.04	3.63	0.97	2.35
Other	1.82	2.00	0.40	1.00	2.00	2.00	NR	0.00	1.67	1.63	0.17	0.60	3.50	3.60	0.46	1.50
Not reported	1.80	2.00	0.41	1.00	1.50	1.50	0.58	1.00	1.69	1.67	0.20	0.71	3.32	3.57	0.86	4.00

Table 3.6.4. Detailed analysis of outcomes by scaffold material. Outcome scores and descriptive statistics for each scaffold material.

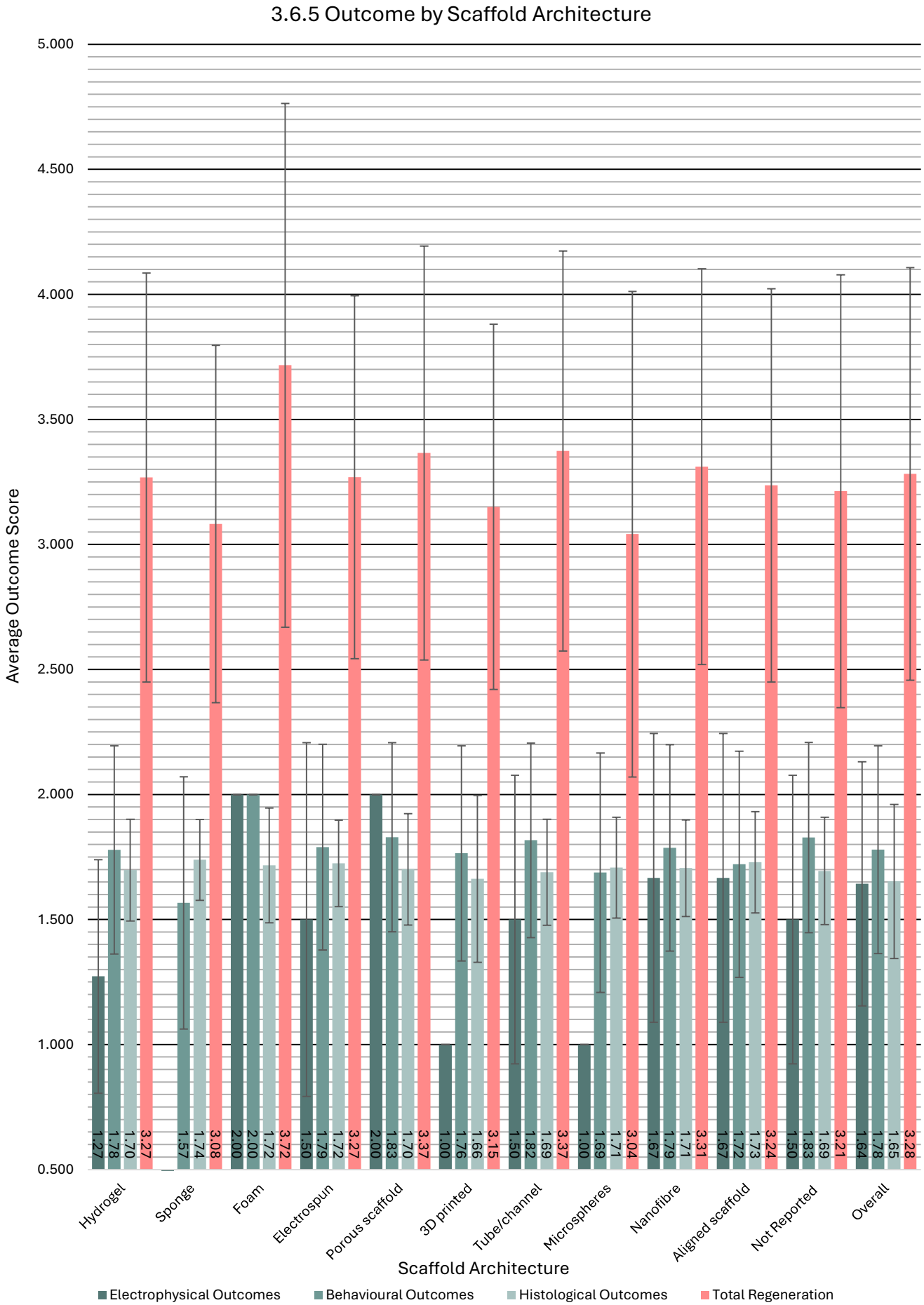

Figure 3.6.5. Average outcome by scaffold architecture. Mean outcome score across outcome domains for each scaffold architecture.

	Behavioural mean	Behavioural median	Behavioural SD	Behavioural range	Electrophysical Mean	Electrophysical Median	Electrophysical SD	Electrophysical Range	Histological mean	Histological Median	Histological SD	Histological range	Total Regeneration Average	Total Regeneration Median	Total Regeneration SD	Total Regeneration Range
Hydrogel	1.78	2.00	0.42	1.00	1.27	1.00	0.47	1.00	1.70	1.71	0.20	1.00	3.27	3.57	0.82	4.75
Sponge	1.57	2.00	0.50	1.00	NR	NR	NR	NR	1.74	1.75	0.16	0.71	3.08	3.00	0.71	2.33
Foam	2.00	2.00	0.00	0.00	2.00	2.00	NR	0.00	1.72	1.80	0.23	0.60	3.72	3.80	1.05	3.57
Electrospun	1.79	2.00	0.41	1.00	1.50	1.50	0.71	1.00	1.72	1.73	0.17	0.67	3.27	3.60	0.73	2.40
Porous scaffold	1.83	2.00	0.38	1.00	2.00	2.00	0.00	0.00	1.70	1.71	0.22	1.00	3.37	3.65	0.83	4.51
3D printed	1.76	2.00	0.43	1.00	1.00	1.00	NR	0.00	1.66	1.67	0.33	2.00	3.15	3.50	0.73	2.60
Tube/channel	1.82	2.00	0.39	1.00	1.50	1.50	0.58	1.00	1.69	1.75	0.21	1.00	3.37	3.61	0.80	4.33
Microspheres	1.69	2.00	0.48	1.00	1.00	1.00	NR	0.00	1.71	1.67	0.20	0.67	3.04	3.50	0.97	3.40
Nanofiber	1.79	2.00	0.41	1.00	1.67	2.00	0.58	1.00	1.71	1.71	0.19	0.86	3.31	3.60	0.79	4.57
Aligned scaffold	1.72	2.00	0.45	1.00	1.67	2.00	0.58	1.00	1.73	1.75	0.20	0.86	3.24	3.50	0.79	4.27
Not Reported	1.83	2.00	0.38	1.00	1.50	1.50	0.58	1.00	1.69	1.67	0.21	0.80	3.21	3.50	0.87	4.67

Table 3.6.6. Detailed analysis of outcomes by scaffold architecture. Outcome scores and descriptive statistics for each scaffold architecture.

Figure 3.6.7. Average outcome by scaffold combination therapy. Mean outcome score across outcome domains for each scaffold combination therapy.

	Behavioural mean	Behavioural median	Behavioural SD	Behavioural range	Electrophysical Mean	Electrophysical Median	Electrophysical SD	Electrophysical Range	Histological mean	Histological Median	Histological SD	Histological range	Total Regeneration Average	Total Regeneration Median	Total Regeneration SD	Total Regeneration Range
Overall	1.78	2.00	0.42	1.00	1.64	2.00	0.49	1.00	1.65	1.67	0.31	1.00	3.28	3.57	0.83	5.00
None	1.79	2.00	0.41	1.00	1.63	2.00	0.52	1.00	1.72	1.71	0.21	1.00	3.32	3.60	0.83	4.86
Cells	1.76	2.00	0.43	1.00	1.29	1.00	0.49	1.00	1.69	1.71	0.23	2.00	3.21	3.50	0.80	4.55
Growth Factor	1.74	2.00	0.44	1.00	1.40	1.00	0.55	1.00	1.73	1.71	0.17	0.71	3.24	3.60	0.92	4.21
Drug/Pharmaceutical	1.74	2.00	0.44	1.00	1.50	1.50	0.71	1.00	1.71	1.75	0.21	0.67	3.20	3.50	0.78	4.17
Growth Factor	1.92	2.00	0.28	1.00	1.50	1.50	0.71	1.00	1.71	1.79	0.24	0.80	3.41	3.71	0.82	3.67
Rehabilitation	1.80	2.00	0.45	1.00	NR	NR	NR	NR	1.78	1.84	0.24	0.60	3.28	3.64	0.94	2.40
Surgical Incision	2.00	2.00	NR	0.00	NR	NR	NR	NR	1.40	1.40	NR	0.00	3.40	3.40	NR	0.00
Biomolecules	1.91	2.00	0.30	1.00	1.50	1.50	0.71	1.00	1.65	1.67	0.27	1.00	3.36	3.67	1.16	4.67
Other Combinations	1.88	2.00	0.34	1.00	NR	NR	NR	NR	1.72	1.69	0.13	0.50	3.39	3.67	0.70	2.25
Multiple (>3)	1.75	2.00	0.44	1.00	1.50	1.50	0.71	1.00	1.63	1.61	0.26	0.86	3.21	3.41	0.69	2.57

Table 3.6.8. Detailed analysis of outcomes by scaffold combination therapy. Outcome scores and descriptive statistics for each scaffold combination therapy.

3.7 Translational Readiness (TR)

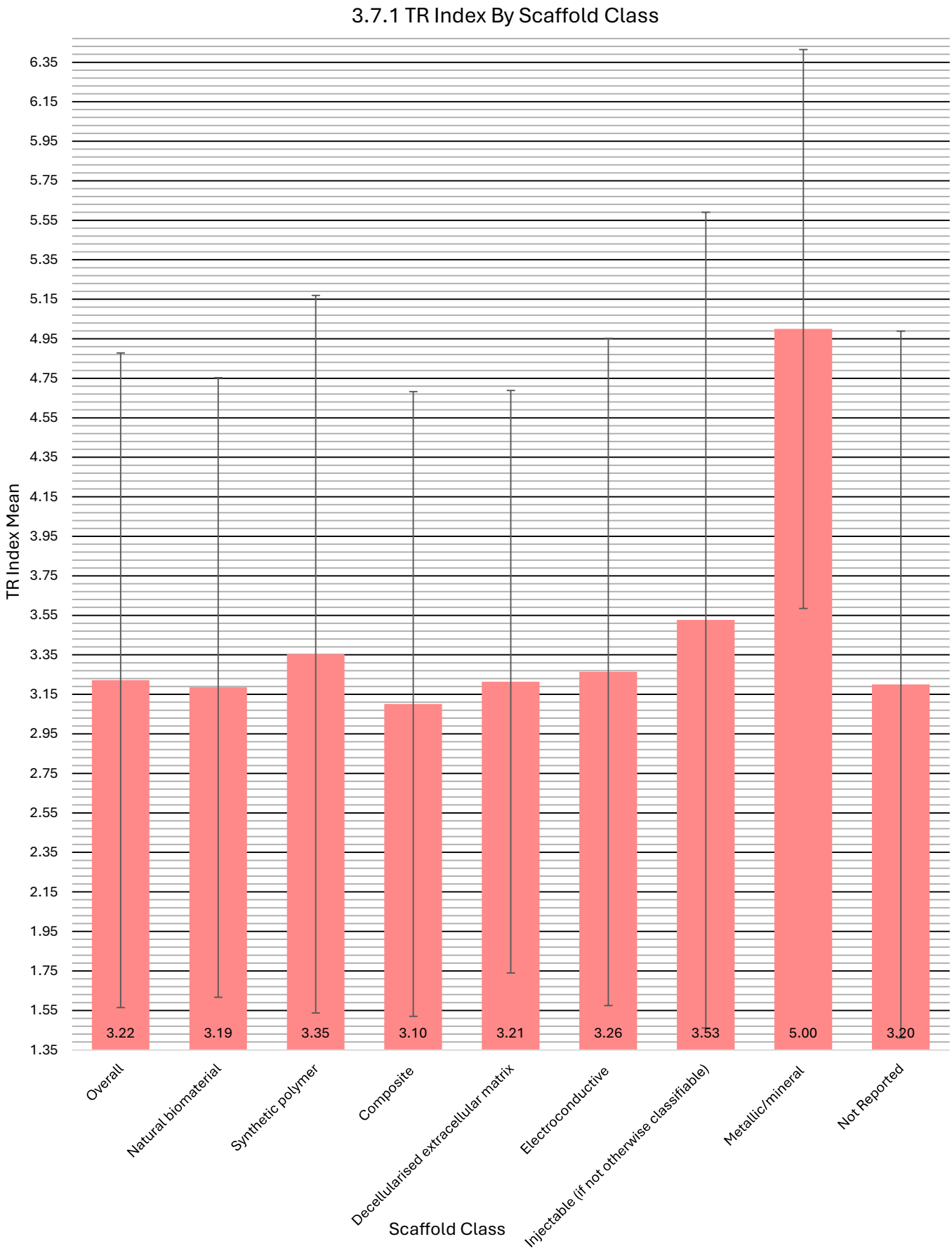

Figure 3.7.1. Average translational readiness by scaffold class. Mean translational readiness score for each scaffold class.

	TR Index Mean	TR Index Median	TR SD	TR index Range
Overall	3.22	3	1.66	c
Natural biomaterial	3.19	3	1.57	8
Synthetic polymer	3.35	3	1.82	9
Composite	3.10	3	1.58	7
Decellularised extracellular matrix	3.21	3	1.47	6
Electroconductive	3.26	3	1.69	9
Injectable (if not otherwise classifiable)	3.53	3	2.06	8
Metallic/mineral	5.00	5	1.41	2
Not Reported	3.20	3	1.79	8

Table 3.7.2. Detailed analysis of translational readiness by scaffold class. Translational readiness scores and descriptive statistics for each scaffold class.

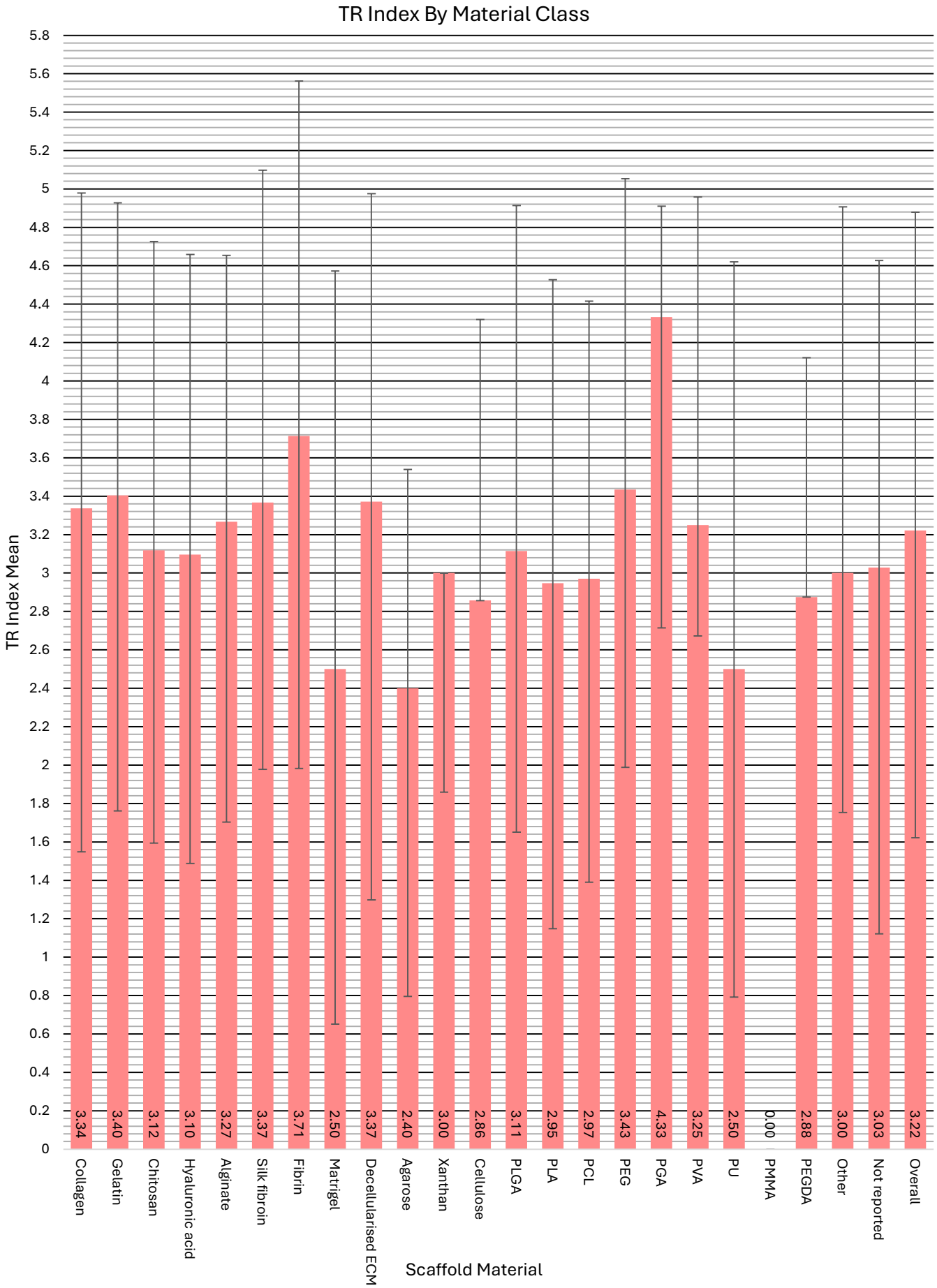

Figure 3.7.3. Average translational readiness by scaffold material. Mean translational readiness score for each scaffold material.

	TR Index Mean	TR Index Median	TR SD	TR index Range
Collagen	3.34	3	1.64	7
Gelatine	3.40	3	1.52	6
Chitosan	3.12	3	1.61	7
Hyaluronic acid	3.10	3	1.56	7
Alginate	3.27	3	1.39	6
Silk fibroin	3.37	3.5	1.73	6
Fibrin	3.71	3	1.85	7
Matrigel	2.50	2.5	2.07	5
Decellularised ECM	3.37	3	1.60	7
Agarose	2.40	2	1.14	3
Xanthan	3.00	3	NR	0
Cellulose	2.86	3	1.46	4
PLGA	3.11	3	1.80	9
PLA	2.95	3	1.58	5
PCL	2.97	3	1.45	6
PEG	3.43	3	1.62	5
PGA	4.33	4	0.58	1
PVA	3.25	3.5	1.71	4
PU	2.50	2.5	2.12	3
PMMA	NR	NR	NR	NR
PEGDA	2.88	2	1.25	3
Other	3.00	2.5	1.91	5
Not reported	3.03	3	1.60	8
Overall	3.22	3	1.66	9

Table 3.7.4. Detailed analysis of translational readiness by scaffold material. Translational readiness scores and descriptive statistics for each scaffold material.

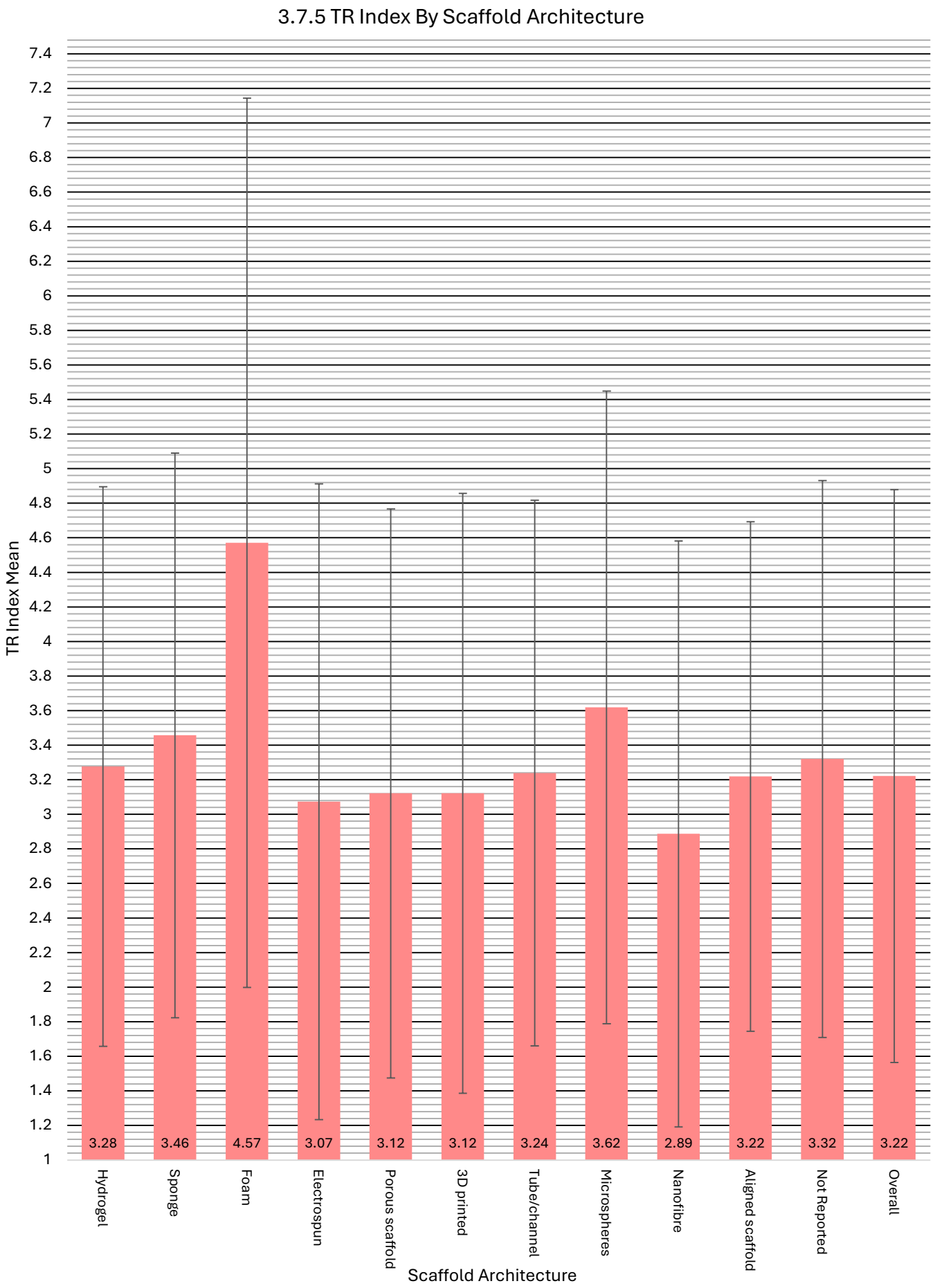

Figure 3.7.5. Average translational readiness by scaffold architecture. Mean translational readiness score for each scaffold architecture.

	TR Index Mean	TR Index Median	TR SD	TR index Range
Hydrogel	3.28	3	1.62	9
Sponge	3.46	3	1.63	5
Foam	4.57	5	2.57	8
Electrospun	3.07	3	1.84	9
Porous scaffold	3.12	3	1.65	9
3D printed	3.12	3	1.73	8
Tube/channel	3.24	3	1.58	7
Microspheres	3.62	3	1.83	6
Nanofiber	2.89	3	1.69	7
Aligned scaffold	3.22	3	1.47	6
Not Reported	3.32	3	1.61	7
Overall	3.22	3	1.66	9

Table 3.7.6. Detailed analysis of translational readiness by scaffold architecture. Translational readiness scores and descriptive statistics for each scaffold architecture.

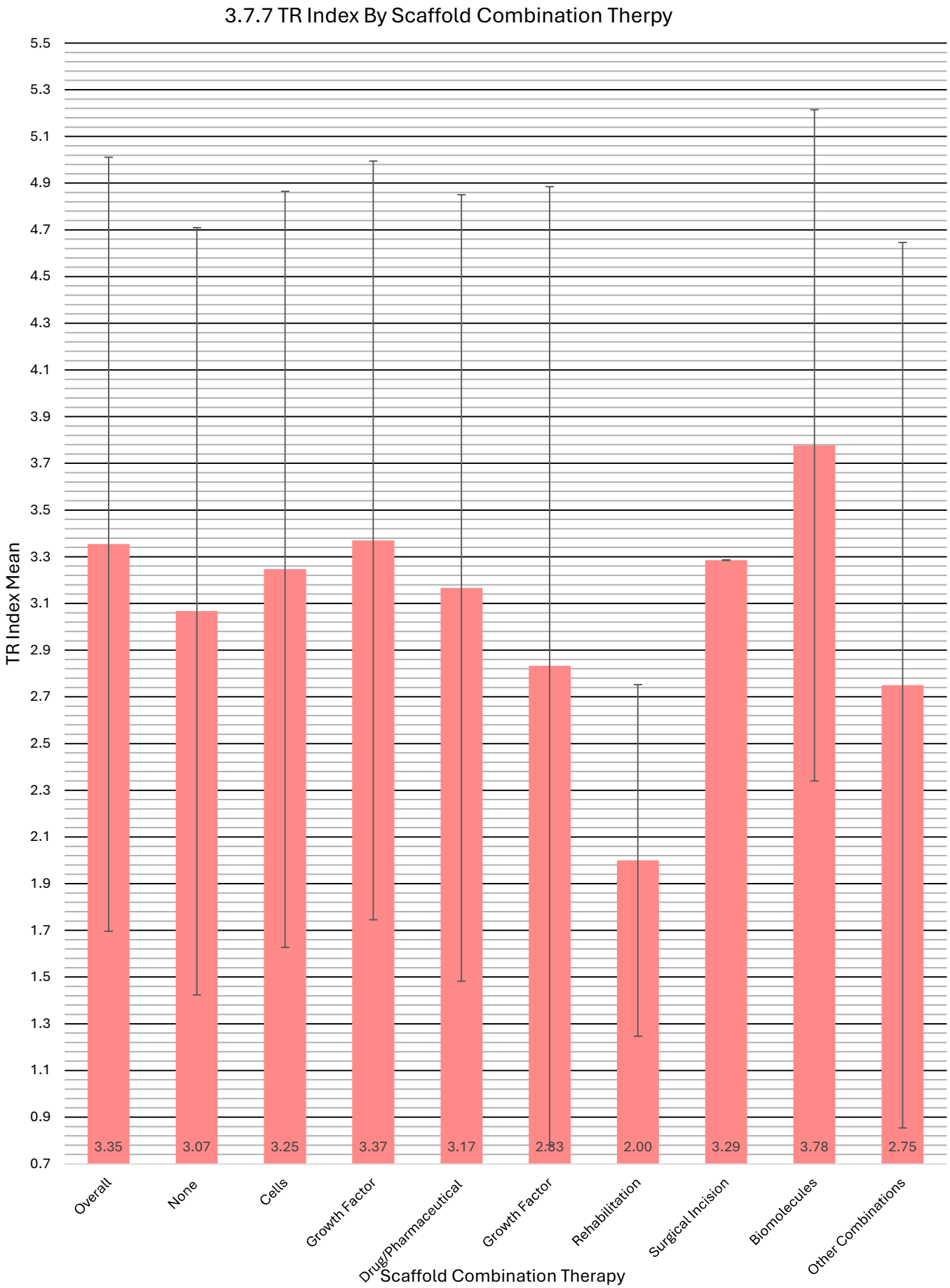

Figure 3.7.7. Average translational readiness by scaffold combination therapy. Mean translational readiness score for each scaffold combination therapy.

	TR Index Mean	TR Index Median	TR SD	TR index Range
Overall	3.22	3	1.66	9
None	3.35	3	1.64	9
Cells	3.07	3	1.62	8
Growth Factor	3.25	3	1.62	8
Drug/Pharmaceutical	3.37	3	1.68	9
Growth Factor	3.17	2	2.05	8
Rehabilitation	2.83	3	0.75	2
Surgical Incision	2.00	2	NR	0
Biomolecules	3.29	3	1.44	5
Other Combinations	3.78	4.5	1.90	7
Multiple (>3)	2.75	2.5	1.92	7

Table 3.7.8. Detailed analysis of translational readiness by scaffold combination therapy. Translational readiness scores and descriptive statistics for each scaffold combination therapy.

3.8 Translational Readiness Domains

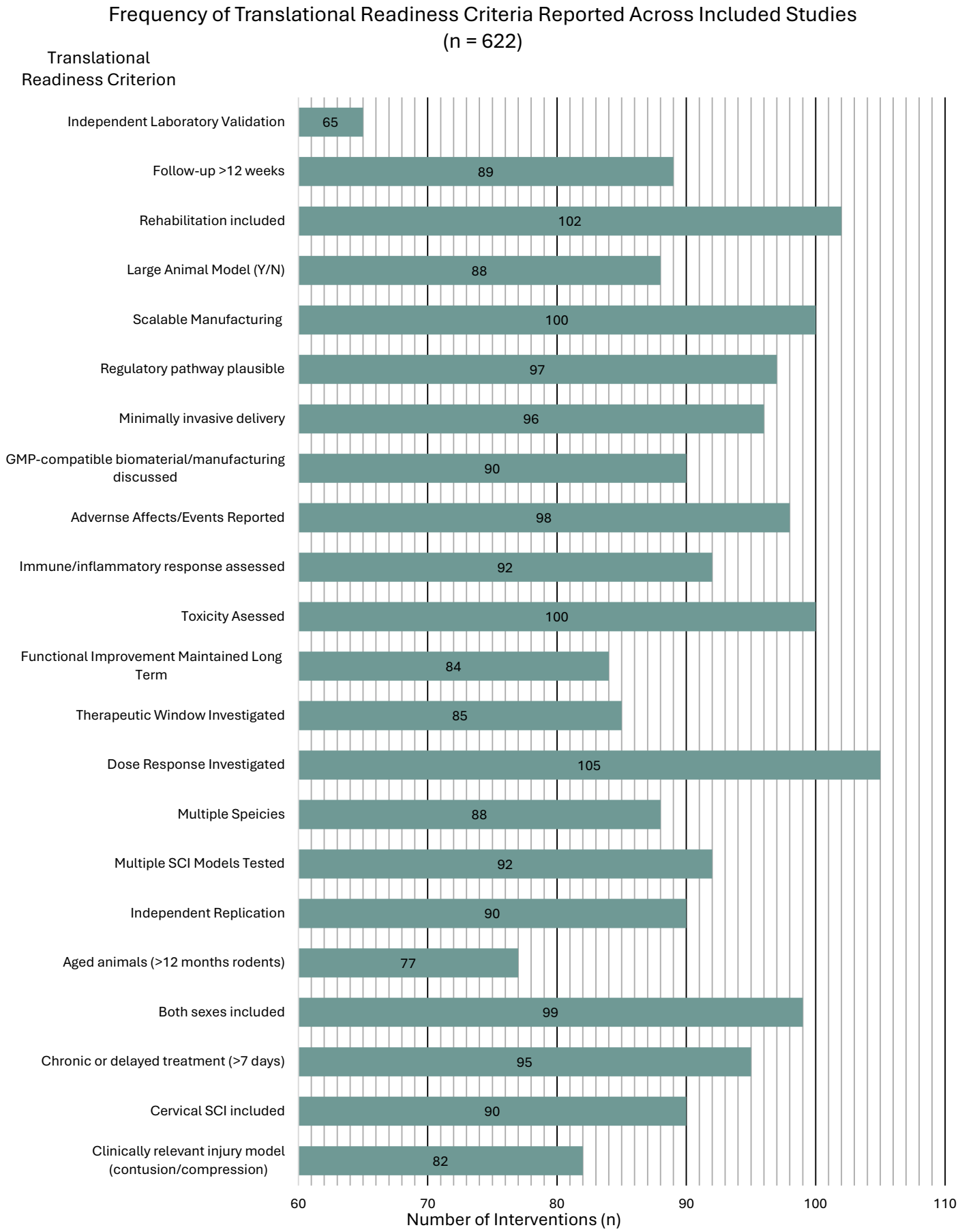

Figure 3.8. Frequency of translational readiness criteria reported across included studies. Frequency with which individual translational readiness criteria were reported across included studies.

3.9 Specific Scaffold Analysis

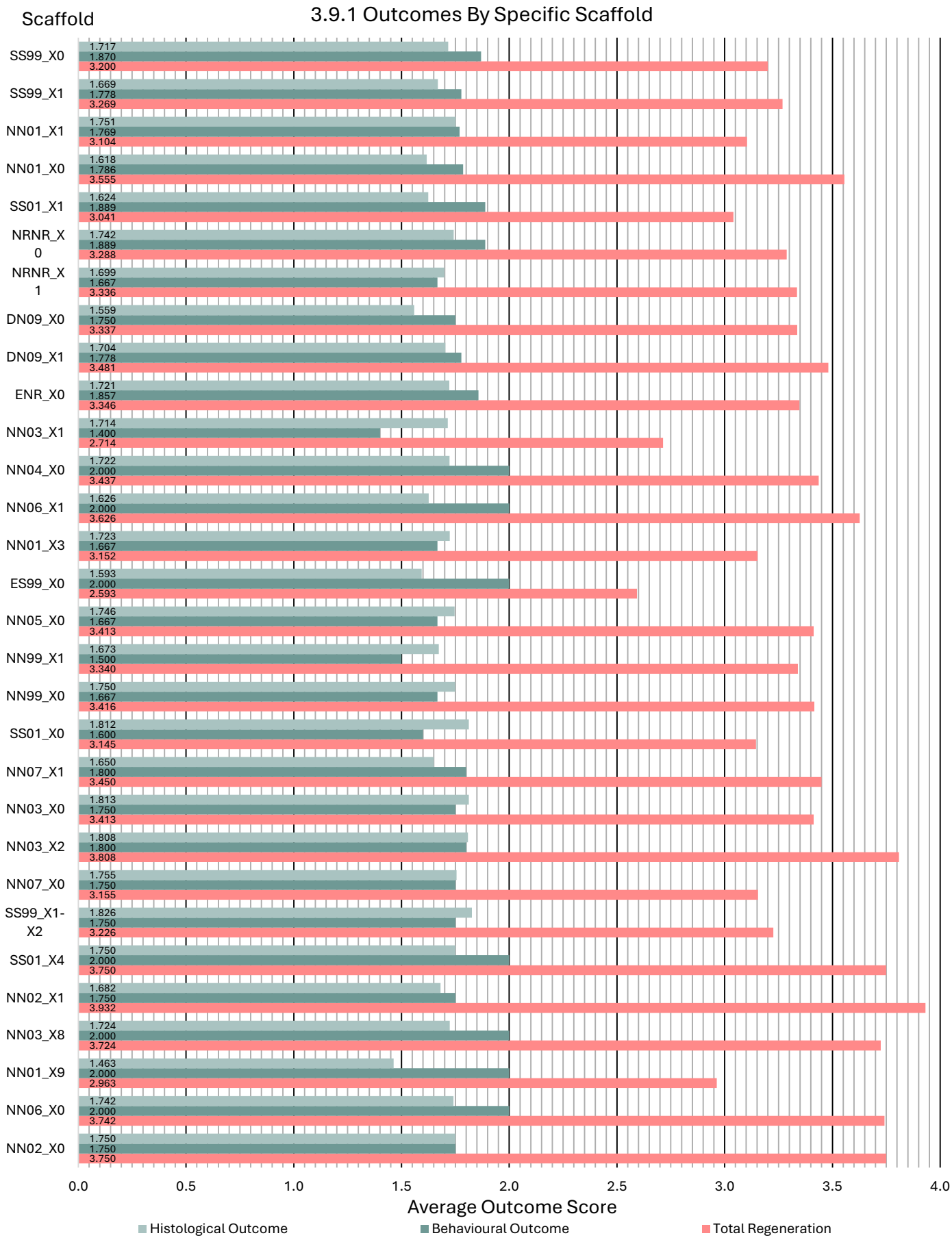

Figure 3.9.1. Outcomes by specific scaffold. Mean outcome scores for individual scaffold types.

Scaffold Type (Labelled)	Number of Interventions	Mean Behavioural Score	Median Behavioural Score	Behavioural score Range	Histological Score Mean	Histological Score Median	Histological Score Range	Electrophysiology Score Mean	Total Regeneration Score Mean	Total Regeneration Score Median	Total Regeneration Score Range	Total Regeneration Score SD
NN02_X0	4	1.750	2.000	1.000	1.750	1.800	0.600	1	3.750	3.700	2.400	1.012
NN06_X0	4	2.000	2.000	0.000	1.742	1.733	0.500	NA	3.742	3.733	0.500	0.211
NN01_X9	4	2.000	2.000	0.000	1.463	1.414	0.225	2	2.963	3.400	2.196	1.029
NN03_X8	4	2.000	2.000	0.000	1.724	1.714	0.133	NA	3.724	3.714	0.133	0.056
NN02_X1	4	1.750	2.000	1.000	1.682	1.792	0.857	2	3.932	3.488	2.750	1.266
SS01_X4	4	2.000	2.000	0.000	1.750	1.833	0.667	NA	3.750	3.833	0.667	0.319
SS99_X1-X2	5	1.750	2.000	1.000	1.826	1.750	0.333	NA	3.226	3.667	1.750	0.752
NN07_X0	5	1.750	2.000	1.000	1.755	1.800	0.500	NA	3.155	3.600	2.500	1.036
NN03_X2	5	1.800	2.000	1.000	1.808	1.833	0.375	1	3.808	3.833	1.625	0.576
NN03_X0	5	1.750	2.000	1.000	1.813	1.800	0.161	1	3.413	3.714	2.925	1.098
NN07_X1	5	1.800	2.000	1.000	1.650	1.667	0.500	NA	3.450	3.667	1.167	0.477
SS01_X0	6	1.600	2.000	1.000	1.812	1.900	0.500	NA	3.145	3.286	2.500	0.904
NN99_X0	6	1.667	2.000	1.000	1.750	1.762	0.500	NA	3.416	3.583	1.400	0.559
NN99_X1	6	1.500	1.500	1.000	1.673	1.667	0.333	1	3.340	3.583	1.262	0.522
NN05_X0	6	1.667	2.000	1.000	1.746	1.774	0.500	NA	3.413	3.536	1.286	0.529
ES99_X0	6	2.000	2.000	0.000	1.593	1.619	0.857	NA	2.593	2.714	2.607	1.123
NN01_X3	7	1.667	2.000	1.000	1.723	1.714	0.500	NA	3.152	3.500	2.250	0.771
NN06_X1	7	2.000	2.000	0.000	1.626	1.800	0.833	NA	3.626	3.800	0.833	0.333
NN04_X0	7	2.000	2.000	0.000	1.722	1.800	0.600	NA	3.437	3.667	2.200	0.751
NN03_X1	8	1.400	1.000	1.000	1.714	1.774	0.433	1	2.714	2.750	2.233	0.793
ENR_X0	8	1.857	2.000	1.000	1.721	1.700	0.500	NA	3.345	3.586	2.000	0.708
DN09_X1	9	1.778	2.000	1.000	1.704	1.750	0.750	NA	3.481	3.500	1.167	0.406
DN09_X0	9	1.750	2.000	1.000	1.559	1.667	1.000	2	3.337	3.600	3.905	1.174
NRNR_X1	11	1.667	2.000	1.000	1.699	1.714	0.500	1.5	3.336	3.500	3.914	1.168
NRNR_X0	11	1.889	2.000	1.000	1.742	1.800	0.667	NA	3.288	3.667	2.250	0.808
SS01_X1	12	1.889	2.000	1.000	1.624	1.613	0.371	NA	3.041	3.500	2.300	0.914
NN01_X0	16	1.786	2.000	1.000	1.618	1.667	0.467	2	3.555	3.611	4.000	0.977
NN01_X1	17	1.769	2.000	1.000	1.751	1.750	0.500	NA	3.104	3.500	2.286	0.820
SS99_X1	20	1.778	2.000	1.000	1.669	1.714	0.800	NA	3.269	3.667	2.800	0.784
SS99_X0	29	1.870	2.000	1.000	1.717	1.714	1.000	NA	3.200	3.667	2.667	0.902

Table 3.9.2. Detailed analysis of outcomes by specific scaffold. Outcome scores and descriptive statistics for individual scaffold types.

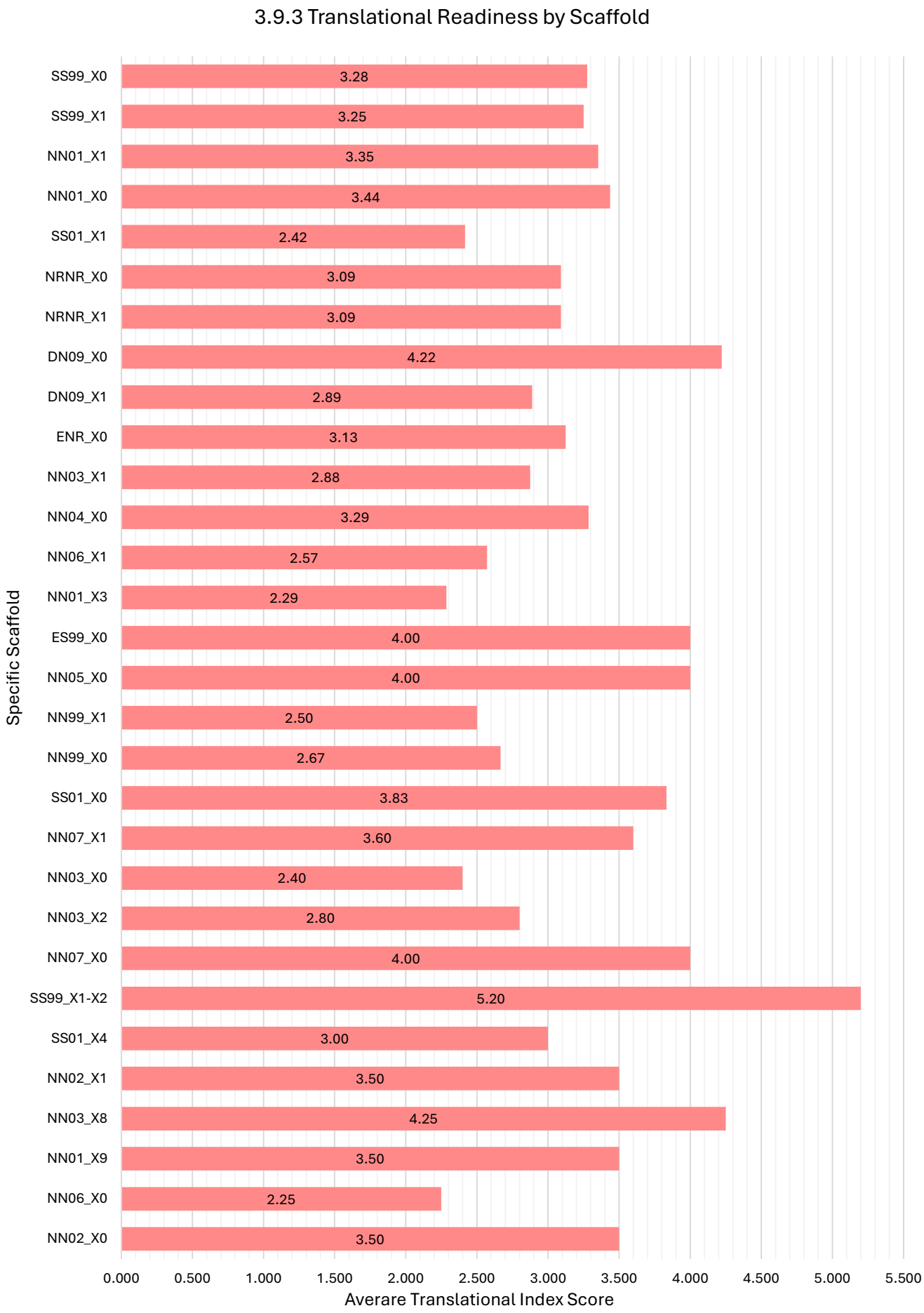

Figure 3.9.3. Translational readiness by specific scaffold. Mean translational readiness scores for individual scaffold types.

Scaffold Type (Labelled)	Transitional Score Mean	Transitional Score Median
NN02_X0	3.500	3.500
NN06_X0	2.250	2.000
NN01_X9	3.500	3.000
NN03_X8	4.250	5.000
NN02_X1	3.500	2.500
SS01_X4	3.000	3.000
SS99_X1-X2	5.200	5.000
NN07_X0	4.000	4.000
NN03_X2	2.800	3.000
NN03_X0	2.400	3.000
NN07_X1	3.600	3.000
SS01_X0	3.833	4.000
NN99_X0	2.667	2.500
NN99_X1	2.500	2.000
NN05_X0	4.000	4.500
ES99_X0	4.000	3.500
NN01_X3	2.286	2.000
NN06_X1	2.571	2.000
NN04_X0	3.286	4.000
NN03_X1	2.875	2.500
ENR_X0	3.125	3.500
DN09_X1	2.889	3.000
DN09_X0	4.222	4.000
NRNR_X1	3.091	3.000
NRNR_X0	3.091	3.000
SS01_X1	2.417	2.000
NN01_X0	3.438	3.500
NN01_X1	3.353	3.000
SS99_X1	3.250	2.500
SS99_X0	3.276	3.000

Table 3.9.4. Detailed breakdown of translational readiness by specific scaffold. Translational readiness scores and descriptive statistics for individual scaffold types.

3.10 Association between Outcome Measures

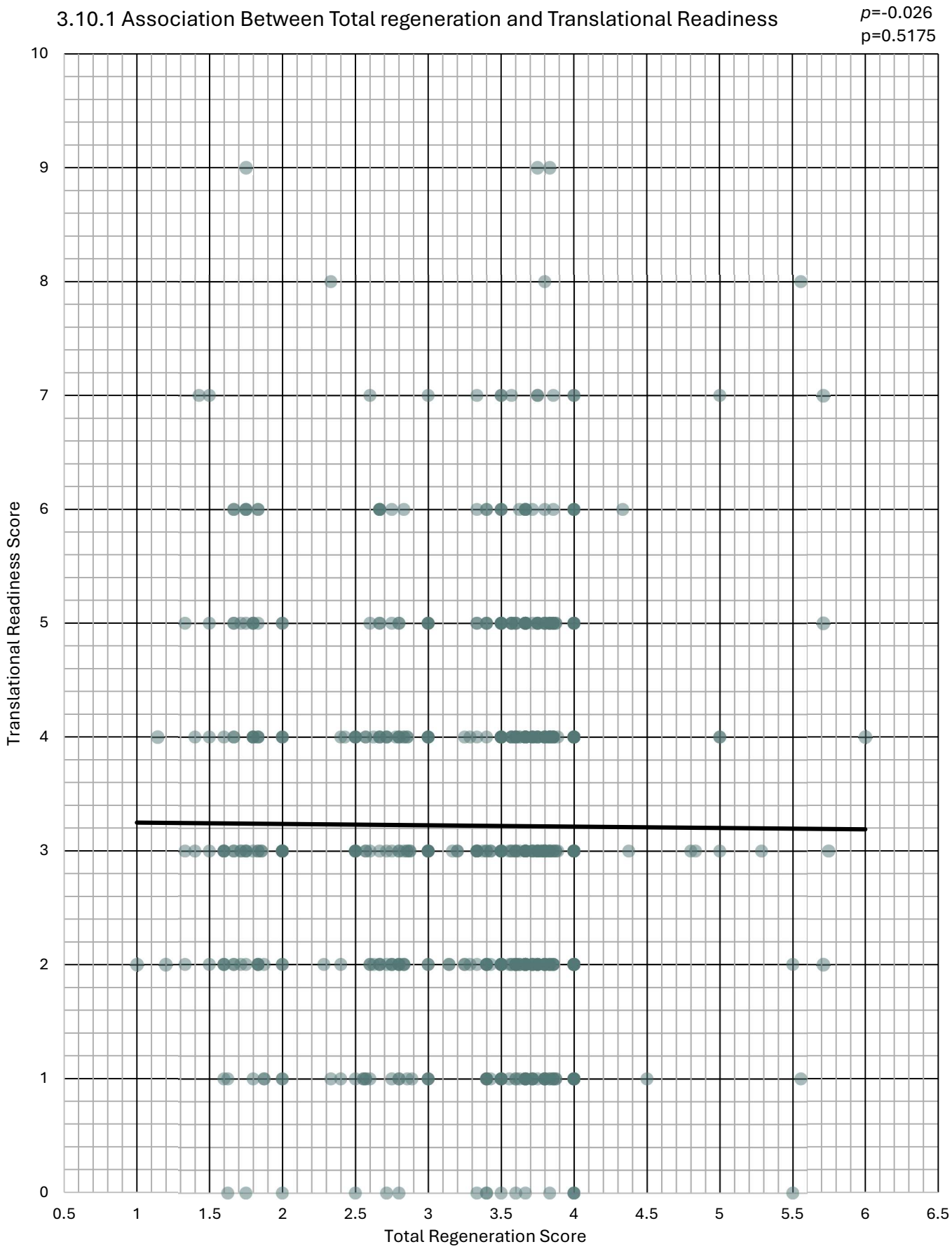

Figure 3.10.1. Association between total regeneration and translational readiness. Association between total regeneration score and translational

3.10.2 Association Between Histological Outcomes and Translational Readiness

p =.0203
p=0.6133

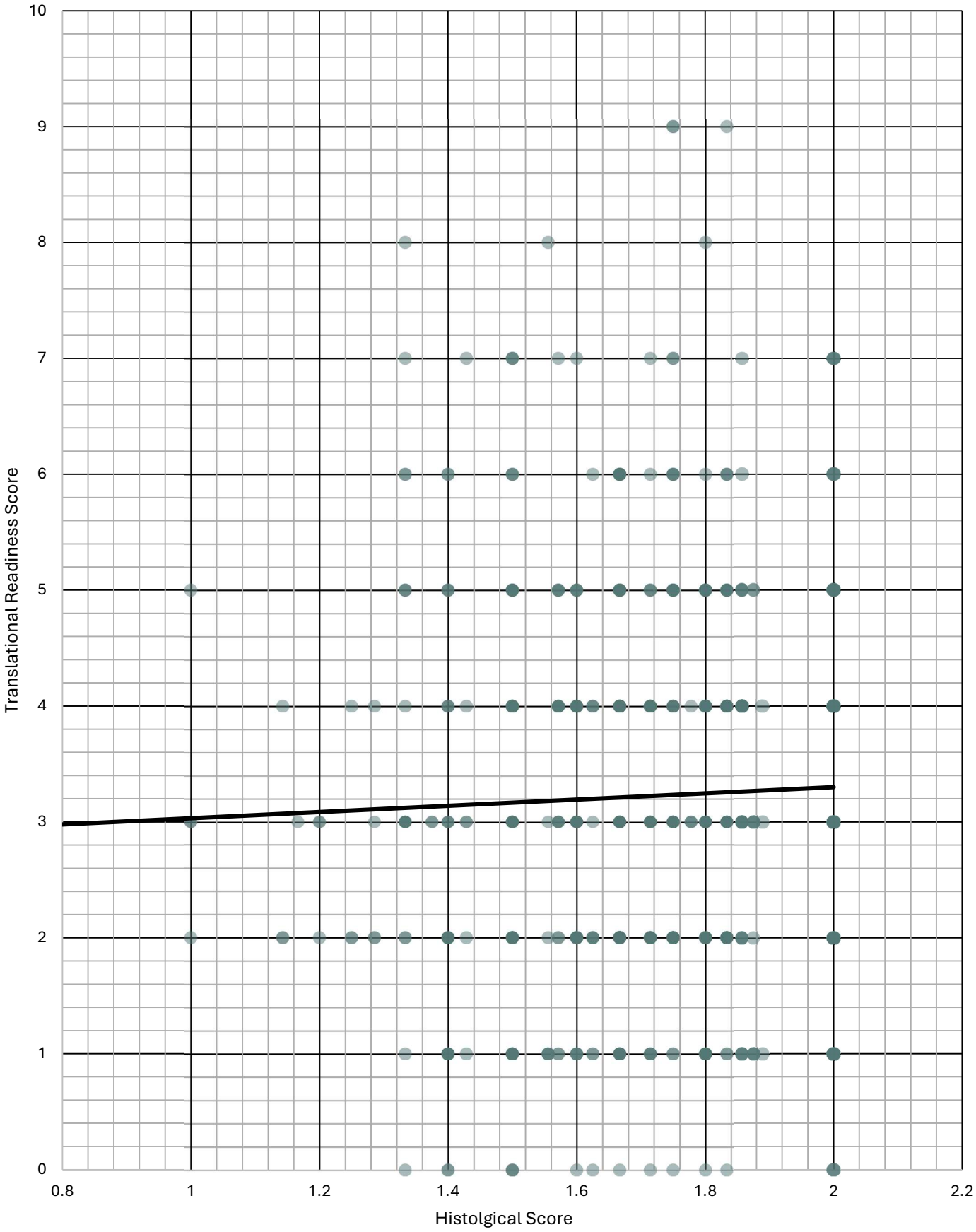

Figure 3.10.2. Association between histological outcomes and translational readiness. Association between histological outcome scores and translational readiness scores across interventions.

3.10.3 Association Between Behavioural Outcomes and Translational Readiness

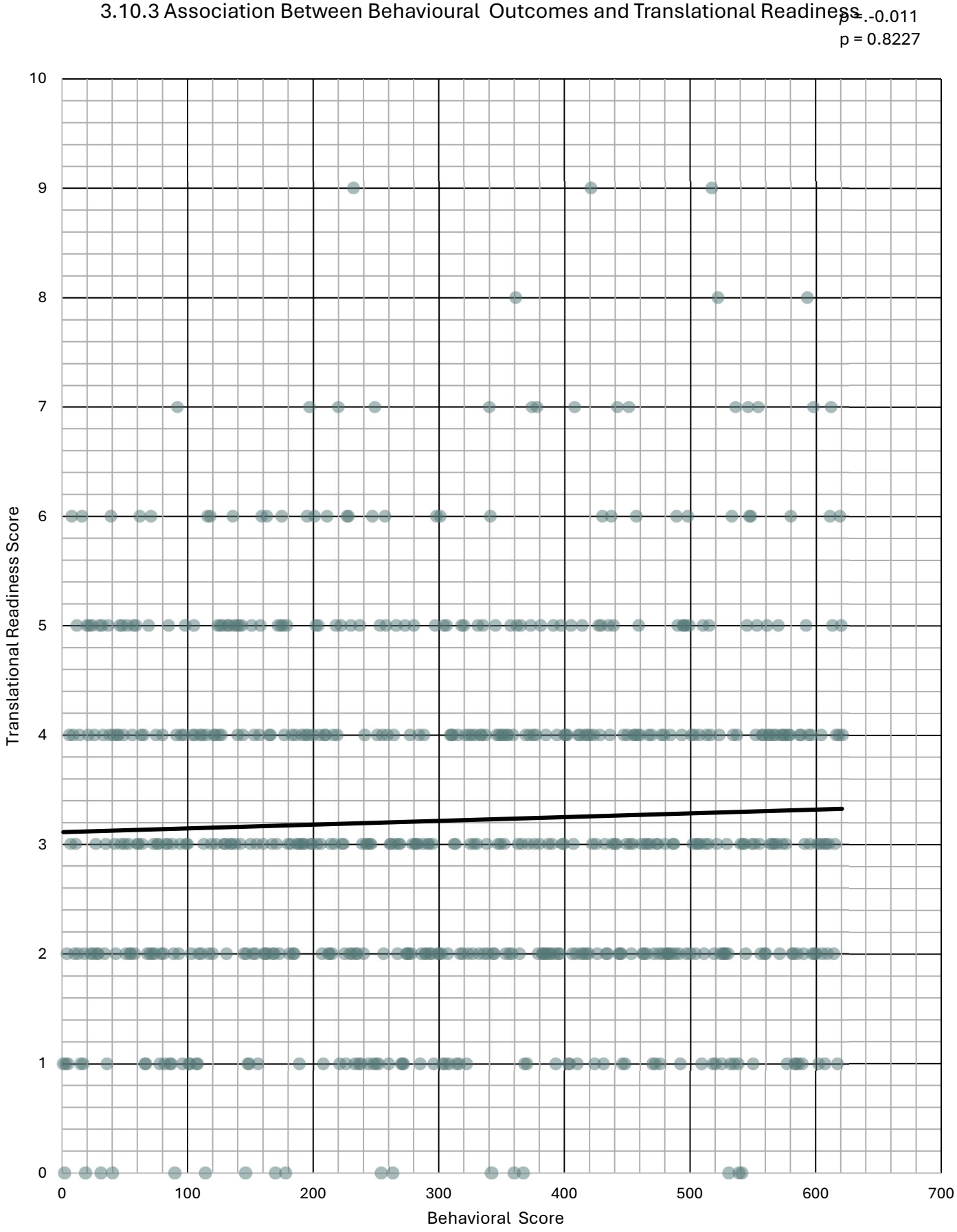

Figure 3.10.3. Association between behavioural outcomes and translational readiness. Association between behavioural outcome scores and translational readiness scores across interventions.

4 Discussion

4.1 Principal Findings

This systematic-review identified 622 in vivo studies investigating scaffold-based tissue-engineering strategies for spinal cord injury (SCI). Across the literature, behavioural and regenerative outcomes were favourable, whereas evidence for physiological recovery, reproducibility and translation was limited. The most important finding was therefore that scaffolds were associated with recovery and that reported regenerative efficacy and translational preparedness were poorly correlated.

Overall behavioural outcomes were strongly favourable, with a mean score of 1.779, median of 2.0 and standard deviation (SD) of 0.415. Total regeneration had a mean of 3.231, median of 3.5 and SD of 0.851. These findings show that positive behavioural and tissue-level outcomes were common across the literature. However, the distribution should not be interpreted as demonstrating a uniform or large treatment effect. The behavioural scoring system was deliberately designed to synthesise highly heterogeneous outcome measures, but its 0–2 scale necessarily compresses information. A study reporting a modest but statistically significant improvement may therefore occupy the same category as one reporting a much larger effect.

Guijarro-Belmar-et-al. included 134 publications evaluating biomaterial-based combination strategies and found that such interventions improved locomotor recovery by 25.3% (95% CI 20.3–30.3; n=102) and in vivo axonal regeneration by 1.6 SD (95% CI 1.2–2.0; n=117) compared with injury-only controls[16]. However, heterogeneity was huge, and biomaterial type did not explain that heterogeneity: for locomotor recovery, I^2 was 90.4% and the effect of biomaterial type was non-significant (p=0.691); for axonal regeneration, I^2 was 77.3% and again biomaterial type did not account for the observed variation (p=0.959).

This is consistent with the present review, broad scaffold classification did not significantly influence behavioural outcome (p=0.875), histological outcome (p=0.793), total regeneration (p=0.981), or translational readiness (p=0.777). The repeated absence of significant class-level differences suggests that the question “Which scaffold material is best?” may simply be too crude. More informative variables are likely to reside in scaffold architecture, mechanical properties, degradation behaviour, biochemical functionalisation, cellular composition and the timing and manner of implantation.

The translational findings were less promising. The Translational Readiness Index (TRI) had a mean of 3.22, median of 3 and SD of 1.657, despite a possible maximum score of 22. Furthermore, TRI was unrelated to behavioural outcome (ρ=-0.010, p=0.814), histological outcome (ρ=0.020, p=0.613) and total regeneration (ρ=-0.009, p=0.832). These coefficients are sufficiently close to zero that there was no evidence in this dataset of even a weak monotonic association between regenerative performance and the collection of predefined translational characteristics.

The field has accumulated a large body of evidence that scaffolds can alter the injured spinal cord and improve experimental recovery, but less evidence that these effects remain robust when experiments are made more clinically realistic.

4.2 The Expanding Evidence Base

The number of included studies increased over the period examined, with 338 of the 622 studies published between 2020-2026. 338 were published from 2020 onwards, indicating that more than half of the evidence base has emerged within approximately the most recent period covered. This expansion reflects the continuing interest in scaffolds as a means of overcoming several barriers to CNS regeneration simultaneously. A scaffold can provide structural support, influence cell adhesion and migration, occupy a lesion cavity, present biochemical cues, and serve as a vehicle for cells or therapeutic molecules. Its appeal lies in replacing lost tissue and in modifying the microenvironment in which regeneration occurs.

Khavandegar-et-al. identified 931 studies concerning bioengineered scaffolds for SCI, 82% of which were in vivo, illustrating the expansion of the field[17]. Their review identified 82 different biomaterials, 27 cell types and 38 bioactive and 88 pharmacological agents, demonstrating considerable heterogeneity in intervention design.

The present findings support this interpretation. The behavioural means of the four substantial scaffold categories differed by only 0.055 points between the lowest and highest groups. Natural scaffolds scored 1.771, synthetic scaffolds 1.780, composites 1.791 and electroconductive scaffolds 1.826. The absence of a significant class effect suggests that the biological behaviour of a scaffold cannot readily be reduced to whether its constituent material is natural or synthetic.

This distinction is important because the results suggest that material identity alone is a poor predictor of outcome. The apparent absence of a class effect should not be interpreted as evidence that biomaterial chemistry is irrelevant; rather, it suggests that the biologically important properties of a scaffold may be distributed across several interacting design variables with the important therapeutic variables operating at a lower level than the broad categories used for classification.

4.3 Behavioural Recovery

Behavioural outcomes were the most consistently reported outcome domain in the present review. The mean score was 1.779, with a median of 2.0 and SD of 0.415, indicating favourable. This is consistent with previous evidence syntheses showing functional improvement following biomaterial-based interventions in experimental SCI.

Krishna-et-al. reported cumulative BBB improvements of 5.93 points (95% CI 2.41–9.45) in transection models and 4.44 points (95% CI 2.65–6.24) in hemisection models following biomaterial-based multimodal interventions. However, they characterised the overall functional improvement as modest and highlighted uncertainty over the relationship between neuronal regeneration and behavioural recovery[17]. Szymoniuk-et-al likewise reported significant functional improvement in all 11 studies included in their review of 3D-bioprinted scaffolds [18]. Wang et al. also found significant improvements in BBB-based motor outcomes following both natural and synthetic scaffold-assisted cell transplantation compared with controls[19].

The agreement between these studies and the present findings should nevertheless be interpreted carefully because the outcome measures are not directly equivalent. Krishna-et-al quantified changes in BBB scores, whereas the present review assigned categorical scores across a much wider range of behavioural measures. A score of 1.779 therefore does not represent an average treatment effect or a 1.779-point improvement in locomotor function. Instead, it indicates that favourable behavioural outcomes were frequently reported.

The median score of 2.0 also limits the resolution of the present scoring system. Because 2 represents the highest category, studies with different magnitudes of improvement may receive the same score. The high mean therefore demonstrates consistency in the direction of reported findings more clearly than it demonstrates the size of the underlying treatment effects.

This distinction is important when interpreting behavioural recovery alongside regeneration. Improved locomotion does not necessarily demonstrate reconstruction of the injured neural circuitry. Functional recovery may result from spared axons, compensatory motor strategies, plasticity, or partial tissue preservation, while histological evidence of axonal growth or remyelination does not necessarily indicate that newly regenerated pathways have formed functional connections.

Publication bias may further contribute to the high frequency of favourable behavioural findings, since studies reporting positive effects may be more likely to reach publication than those reporting null or adverse results. The present analysis cannot formally quantify this possibility because it does not pool comparable effect sizes. Nevertheless, the consistency of favourable behavioural scores should be interpreted as evidence of a strong experimental efficacy signal, rather than proof of a uniformly large treatment effect.

4.3.1 Histological Recovery and the Problem of Equating Structure with Function

Histological outcomes were favourable and contributed strongly to the total regeneration score, which had a mean of 3.231, median of 3.5 and SD of 0.851. The agreement between behavioural and histological findings is encouraging because functional improvement accompanied by evidence of tissue preservation, axonal growth, remyelination or reduced lesion pathology is more persuasive than either domain alone.

There remains, however, a gap between anatomical repair and restoration of function. Axonal density does not demonstrate that newly extending axons have established appropriate synaptic connections. GAP-43 expression, reduced cavity volume, or increased myelin-associated markers may indicate regeneration, tissue preservation or remyelination without demonstrating functional connectivity.

Only 28 studies (4.5%) reported electrophysiological outcomes, leaving physiological evidence available in only a small proportion of the evidence base.

Szymoniuk-et-al reached a similar conclusion in their systematic review of 3D-bioprinted scaffolds[18]. All 11 included studies reported significant functional improvement, with corresponding histological changes at the injury site; nevertheless, the authors concluded that evidence from other experimental SCI models was required before clinical translation. The present findings suggest that similar caution is warranted when interpreting physiological recovery.

4.3.2 Total Regeneration and the Value, and Danger, of Composite Scoring

The total regeneration score had a mean of 3.231, median of 3.5 and SD of 0.851. Combining domains reflects the multidimensional nature of SCI recovery, but composite scoring can conceal missing evidence. Because electrophysiology was reported by only 28 studies, the score is driven by behavioural and histological findings. A high composite score therefore cannot be interpreted as demonstrating behavioural, anatomical, and physiological recovery simultaneously.

The SD of 0.851 indicates variation around the mean but does not have the same statistical meaning as the SD of a continuous measure such as BBB score because the total regeneration score is an ordinal synthesis of multiple domains. The appropriate interpretation is therefore descriptive: regeneration-related outcomes were favourable, but evidence remained uneven across outcome types.

4.4 Composite Class and Material Specific Findings

The lack of significant differences between scaffold classes is a useful negative finding. Behavioural outcome did not differ significantly by class ($p=0.875$), histological outcome did not differ significantly ($p=0.793$), total regeneration did not differ significantly ($p=0.981$), and TRI did not differ significantly ($p=0.777$).

The descriptive values nevertheless warrant discussion. Natural scaffolds had a behavioural mean of 1.771; synthetic polymers 1.780; composites 1.791; electroconductive scaffolds 1.826. Electroconductive scaffolds therefore had the highest mean among the adequately represented classes, but the difference from natural scaffolds was only 0.055 points. Without a significant class effect, it would be inappropriate to describe electroconductive scaffolds as superior.

The metallic/mineral category provides an even clearer statistical warning. Its mean of 2.0 appears optimal but was based on only two studies. A subgroup of $n=2$ cannot support a reliable estimate of population-level superiority and should instead be regarded as an observation requiring further evidence.

PLGA was represented in 61 studies and had a behavioural mean of 1.784. Gelatine appeared in 52 studies with a mean of 1.826, while hyaluronic acid appeared in 52 studies with a mean of 1.841. These values are all high and relatively close together. The greater frequency of PLGA studies should not be confused with greater efficacy; a material may dominate the literature because of availability, established manufacturing methods, prior evidence, or research tradition.

The agreement with Wang-et-al is reassuring because the two analyses approach the question differently[19]. The present review contains a broader range of scaffold studies and uses categorical outcome scoring, whereas Wang et al. focused on scaffold-guided cell transplantation in rats and used quantitative BBB data. Their similar findings strengthen the argument that broad natural-versus-synthetic classification is unlikely to identify a universally superior material.

4.5 Material Class: The Wrong Level of Comparison

The failure of scaffold class to predict outcome does not mean that scaffold composition is unimportant. It may instead indicate that classification at the material level is too coarse. Tissue engineering is not simply a question of what a scaffold is made from; it is also a question of how the material behaves in three dimensions.

Mechanical stiffness, porosity, degradation kinetics, fibre orientation, electrical conductivity, surface chemistry, and biochemical functionalisation can all alter cellular behaviour. Once these variables are combined with cell transplantation or growth-factor delivery, the therapeutic construct becomes considerably more complex than its material label suggests.

Fibre alignment can provide directional guidance for axonal growth. Porosity influences cell infiltration and nutrient diffusion. Channel architecture can constrain regeneration along anatomically meaningful trajectories. Mechanical stiffness can alter cell behaviour and differentiation. Degradation rate determines how long the scaffold remains available and whether its breakdown products affect the surrounding tissue. These variables may explain why apparently similar materials can produce markedly different outcomes.

A composite may combine several biomaterials because each addresses a different limitation of the others. A natural component might provide biological cues while a synthetic component supplies mechanical stability. An electroconductive component might be added to enable neural signalling. The resulting intervention cannot meaningfully be reduced to a single material category.

The null findings become more convincing when considered alongside previous quantitative evidence. Wang-et-al analysed 25 studies of scaffold-assisted cell transplantation in SCI rats[19]. Natural scaffolds improved BBB scores compared with controls by an MD of 6.0 (95% CI 4.8–7.2), while synthetic scaffolds improved them by 5.7 (95% CI 3.7–7.7). However, the direct comparison between natural and synthetic scaffolds was non-significant (MD −0.80, 95% CI −3.8 to 2.2), and the network estimate likewise found no significant difference (MD −0.35, 95% CI −2.6 to 1.9). Their subgroup analysis also found that cell number was significantly associated with efficacy in the natural-scaffold cohort ($p<0.01$), while cell type and immunosuppressant use influenced outcomes in the synthetic cohort. No single scaffold category therefore explained all the between-study variation.

The broader Guijarro-Belmar-et-al meta-analysis reaches a similar conclusion[16]. Although biomaterial-based combination strategies significantly improved locomotor recovery overall, biomaterial type did not explain the considerable heterogeneity between studies. This suggests that scaffold efficacy is likely to depend on the properties and components of the entire intervention rather than material identity alone. That interpretation is consistent with the breadth of the recent literature. Khavandegar-et-al. identified 82 biomaterials across 931 studies, alongside extensive variation in cells and bioactive agents [11].

The question is therefore probably not whether collagen, PLGA, hyaluronic acid or another material is intrinsically "best." Therapeutic performance may depend more on architecture, stiffness, degradation profile, surface chemistry, conductivity, biochemical cues and interactions with host and transplanted cells.

Future comparisons would therefore benefit from separating material composition from functional characteristics. "Are natural scaffolds better than synthetic scaffolds?" may be less informative than asking whether aligned architecture improves axonal regeneration independently of material type, or whether electrical conductivity improves physiological recovery when architecture and cellular therapy are otherwise comparable.

The present analysis cannot answer these questions directly, but its null class-level findings indicate why they should be asked.

4.6 Combination Therapies

Combination strategies formed a substantial component of the literature. Cells, growth factors, drugs, exosomes, nanoparticles, gene therapy, and electrical stimulation were frequently incorporated into scaffold systems.

The rationale is strong. SCI is not a single pathological process. Tissue loss, inflammation, excitotoxicity, vascular disruption, inhibitory extracellular matrix, glial scarring, axonal degeneration and impaired remyelination occur at distinct stages and interact with one another. A scaffold can provide structural support while transplanted cells supply trophic factors or replace lost cellular populations; growth factors can further modify the local environment.

Previous systematic evidence supports the efficacy of these approaches. Guijarro-Belmar-et-al found that biomaterial-based combination therapies improved locomotor recovery by 25.3% and axonal regeneration by 1.6 SD relative to injury-only controls[16]. More recent evidence is even stronger within specific scaffold categories. Khodaei-et-al. reported a large, pooled effect of decellularised biological scaffolds on motor recovery (SMD=2.6, 95% CI 1.88–3.31; $p<0.0001$), with an even larger effect when scaffold implantation was combined with cell therapy (SMD=2.00, 95% CI 1.21–2.79; $p<0.0001$)[20].

The present findings fit this general pattern. These results should nevertheless be interpreted within their respective scopes. A large, pooled effect in a decellularised-scaffold meta-analysis does not establish that cell combination therapy is superior across all scaffold technologies. It does, however, strengthen the biological case for investigating synergistic combinations.

However, combination therapy introduces a major interpretive problem: which component produced the effect?

Suppose scaffold + cells + growth factor produces a substantial BBB improvement. Without scaffold-only, cell-only, and appropriate combination controls, the contribution of each component remains uncertain. The more elaborate the intervention becomes, the more difficult mechanistic attribution becomes.

Combination therapy also complicates translation. Each additional component introduces considerations relating to dose, storage, sterility, manufacturing, stability, and regulatory classification. A biologically sophisticated construct may therefore be harder to develop than a simpler scaffold with a slightly smaller experimental effect.

This creates an uncomfortable but important possibility: the most impressive intervention in an animal experiment may not be the most clinically viable intervention. The biology favours complexity: clinical development often favours simplicity.

4.7 Translational Readiness

The TRI results provide perhaps the strongest argument for caution.

The mean TRI was 3.22, median 3 and SD 1.657 out of a possible 22. Several translational criteria were uncommon: only 16.9% of studies assessed dose-response, 16.4% incorporated rehabilitation, 16.1% assessed toxicity, 16.1% considered scalable manufacturing, 15.9% included both sexes, approximately 12.4% used aged animals, and only 10.5% involved independent laboratory validation. Approximately 15.3% investigated chronic or delayed treatment, while only around 14% extended follow-up beyond 12 weeks.

Together, these findings indicate a clear translational gap. Most experiments appear designed primarily to establish whether an intervention can produce an effect under controlled conditions. Far fewer examine whether that effect persists under conditions resembling clinical treatment.

Previous systematic reviews identify similar weaknesses. Verstappen et al. identified 393 publications representing 404 experiments and 149 unique animal models, highlighting inconsistencies in animal-model selection, poor reporting, replication, and clinical relevance. Szymoniuk et al. likewise found that all 11 studies in their 3D-bioprinting review used rat transection models and concluded that evidence from other experimental SCI models was needed before clinical translation.

4.7.1 Rat dominance and External Validity

Rats accounted for 583 of the 622 included studies (93.7%), while mice were used in 22 and only 17 studies involved other species. This concentration is understandable: rats offer established behavioural assessments, manageable surgical anatomy, and well-characterised SCI models.

The problem is not the use of rats itself, but the limited diversity of models. Repeated success within one species and injury paradigm demonstrates reproducibility under those conditions more readily than generalisability to human SCI.

Verstappen-et-al identified 404 experiments across 149 unique animal models and highlighted the importance of animal-model selection for biomaterial efficacy and translation[12]. Mid-thoracic rat models were particularly common, reinforcing the concentration observed in the present review.

Szymoniuk-et-al found an even greater concentration within 3D-bioprinting research: all 11 included studies used rat transection models[18]. They consequently argued that other experimental SCI models were needed before clinical translation.

Human SCI varies in injury level, severity, completeness, mechanism, age, and treatment timing. An intervention assessed in an acute experimental transection may therefore behave differently in the heterogeneous and often chronic injuries encountered clinically. Greater use of mice, larger animals and varied injury models would provide a stronger test of whether promising scaffold effects extend beyond the model in which they were first demonstrated.

4.7.2 Treatment Timing

Treatment timing was another translational weakness. Only approximately 15.3% of studies investigated chronic or delayed treatment. This is important because the injured spinal cord changes over time. The acute phase involves haemorrhage, excitotoxicity, vascular dysfunction, and inflammation, whereas later stages are characterised by established scar tissue, altered extracellular matrix, chronic inflammation, tissue cavitation, and reorganised neural circuits.

An intervention that primarily limits secondary injury may therefore appear highly effective when administered immediately but have less relevance to patients treated later. Guijarro-Belmar-et-al reached a similar conclusion, noting that most studies implanted biomaterials during the acute phase and calling for greater use of subacute and chronic models[16].

Khodaei-et-al provide a particularly clear example. Immediate implantation of decellularised biological scaffolds within 30 minutes of SCI produced a large significant effect on motor recovery (SMD=2.54, $p<0.0001$), whereas implantation after 24 hours produced a non-significant effect (SMD=0.903, $p=0.38$)[20]. This does not establish that immediate treatment is inherently superior. Rather, it suggests that timing may modify treatment efficacy and should therefore be examined explicitly.

The translational problem is straightforward: patients do not ordinarily receive regenerative scaffolds within minutes of injury. Transfer, imaging, stabilisation, surgical decision-making, and eligibility assessment inevitably introduce delays. Evidence based almost entirely on immediate-treatment models therefore leaves an important clinical question unanswered: does the intervention still work when treatment begins at a clinically realistic time?

4.7.3 Follow-up Duration and Durability

Long-term follow-up is particularly important for degradable scaffolds because the therapeutic environment changes as the material disappears. Ideally, regenerated tissue should eventually function without the scaffold rather than only while it remains physically present.

Only approximately 14% of studies followed animals for more than 12 weeks, limiting conclusions about durability. Early behavioural recovery may reflect temporary effects such as reduced inflammation, tissue preservation, enhanced trophic signalling or improved transplanted-cell survival, none of which necessarily indicates stable reconstruction of functional neural circuitry.

Degradation further complicates interpretation. As the scaffold breaks down, its mechanical properties change, degradation products disperse, cells migrate into the construct and host tissue remodels around it. Any incorporated therapeutic agent may also cease to be delivered. A short follow-up can therefore capture the period when the scaffold has its greatest effect without showing whether recovery persists after the construct has degraded.

The limited frequency of extended follow-up in the present dataset therefore weakens claims of durable regeneration. An intervention that improves BBB scores at four weeks is encouraging; maintaining that improvement six months later is considerably more persuasive.

4.7.4 Sex and Age

Only 15.9% of studies included both sexes, while approximately 12.4% involved aged animals. The predominance of young animals is understandable, as they provide more controlled experimental conditions and reduce biological variability.

However, this becomes more problematic as interventions move towards translation. Age can affect inflammatory responses, regenerative capacity, vascular function, and tissue properties, while sex can influence immune and injury responses. An intervention that remains effective across these biological differences provides stronger evidence than one tested predominantly in young animals of a single sex.

The low frequency of both sexes and aged animals contributed to the low TRI and suggests that much of the literature remains focused on proof-of-concept efficacy. Once an intervention shows promise, it should be assessed under increasingly heterogeneous conditions to determine whether its effects are reproducible beyond the idealised experimental model.

4.8 Electrophysiology

Only 28 studies reported electrophysiological outcomes, representing approximately 4.5% of the included evidence base. This is important because electrophysiology tests whether preserved or regenerated tissue can actually transmit neural signals.

Axonal growth does not necessarily indicate appropriate synaptic integration, while tissue preservation does not demonstrate restored conduction across the lesion. Behavioural improvement can also arise from plasticity within spared pathways without regeneration across the injury site.

The scarcity of electrophysiological assessment therefore limits claims that scaffold interventions restore functional neural circuitry. Most studies demonstrate either improved behaviour or favourable histological changes; far fewer show that neural signals can cross the injured region.

This also warrants caution when interpreting the total regeneration score. Because electrophysiology was reported so infrequently, the composite is driven mainly by behavioural and histological findings. A high score therefore cannot be interpreted as simultaneous evidence of behavioural, anatomical, and physiological recovery.

4.9 Methodological Quality and Risk of Bias

The SYRCLE assessment revealed substantial uncertainty in methodological reporting. Baseline characteristics were unclear in 71.1% of studies, statistical analysis in 69.9%, animal losses in 69.9%, cage-position randomisation in 68.8%, allocation concealment in 68.5% and outcome-assessor blinding in 67.4%.

These findings require caution. “Unclear risk” does not mean “high risk”: when a study does not report whether outcome assessment was blinded, for example, the review cannot assume that blinding was absent. The main concern is therefore limited reporting and the resulting difficulty in judging study quality. ARRIVE 2.0 was developed to improve transparency in animal research, covering experimental design, sample size, randomisation, blinding, exclusions, and statistical analysis. Adequate reporting allows studies to be scrutinised, reproduced and assessed more reliably[21].

Previous scaffold-specific reviews report similar problems. Szymoniuk-et-al. classified seven of 11 3D-bioprinting studies as having medium risk of bias, three as substantial risk and one as minimal risk, with an overall ARRIVE quality ratio of 0.60, indicating average reporting quality[18]. Verstappen-et-al. likewise identified reporting and reproducibility concerns in biomaterial SCI research[12]. The agreement across reviews suggests that methodological uncertainty reflects a wider problem within the field rather than a result of the present review. Improving reporting would not necessarily improve the underlying experiments, but it would make their reliability far easier to judge.

4.10 Replication and Possibility of Centre Specific Effects

Independent replication was reported in only 10.5% of studies. This may be more consequential than several individual translational criteria because it assesses whether findings remain reproducible outside the original research environment. An impressive result from one laboratory may partly reflect technical expertise, surgical skill, animal husbandry, scaffold fabrication, or other procedural details. If the effect cannot be reproduced elsewhere, confidence in its generalisability falls. Szymoniuk-et-al. similarly noted that some of their 3D-bioprinting studies originated from the same scientific centre[18].

Therefore, hundreds of positive studies do not necessarily represent hundreds of independent demonstrations of efficacy. Repeated experiments from related research environments may provide less evidence than the study count suggests.

This is particularly relevant for complex scaffolds. Fabrication parameters can affect pore structure, stiffness, degradation, and cell distribution, meaning that two laboratories using the same nominal material may produce meaningfully different constructs. Independent replication is therefore essential for determining whether reported effects arise from the intervention itself rather than laboratory-specific methods.

4.11 Dose, safety and manufacturing are underdeveloped.

Approximately 16.9% of studies assessed dose-response relationships, while only 16.1% assessed toxicity and 16.1% considered scalable manufacturing.

These criteria highlight the difference between demonstrating experimental efficacy and developing a viable therapy. A single effective dose does not establish the therapeutic window or indicate when toxicity becomes unacceptable. Similarly, functional improvement does not demonstrate safety. Biomaterials may provoke inflammation, alter local tissue mechanics, release degradation products, or interact unpredictably with transplanted cells.

Manufacturing presents a separate challenge. A scaffold fabricated individually in a research laboratory may be difficult to produce consistently at clinical scale while maintaining its dimensions, porosity, sterility, and mechanical properties.

The low frequency of these assessments helps explain the low TRI despite generally favourable efficacy findings. The literature remains far more focused on demonstrating whether an intervention can work than on establishing how it can be dosed, manufactured, and used safely in patients.

4.12 Efficacy-Translation

The correlations between TRI and regenerative outcomes were effectively zero. Behavioural outcome versus TRI produced ρ=-0.010 (p=0.814), histological outcome ρ=0.020 (p=0.613), and total regeneration ρ=-0.009 (p=0.832). Within this dataset, higher translational-readiness scores were therefore not associated with better regenerative outcomes, nor did stronger regenerative findings coincide systematically with greater translational development.

Several explanations are possible. Translationally oriented studies may simply not produce larger experimental effects. Alternatively, efficacy and translation may have developed as largely separate objectives within the preclinical literature. Experiments designed to maximise detection of a biological effect often use highly controlled conditions, whereas translation introduces additional demands that may expose weaknesses hidden under those conditions. The intervention must remain effective across biological variation, clinically realistic treatment windows, and longer follow-up, while also demonstrating appropriate dosing, safety, manufacturing feasibility, and reproducibility across independent laboratories. Each requirement creates another opportunity for an apparently promising intervention to reveal limitations or lose efficacy.

The absence of correlation therefore does not imply that translational characteristics are unimportant. Rather, it suggests that efficacy and translational development have not necessarily progressed in parallel. Positive regenerative findings have accumulated across a large preclinical evidence base without a corresponding association between regenerative performance and the characteristics needed to support clinical application.

The TRI itself also requires cautious interpretation because it was developed specifically for this review and has not been independently validated as a predictor of clinical success. Its main value is organisational and comparative: characteristics such as model relevance, functional evidence, safety, clinical feasibility, and independent validation can be assessed using predefined criteria across a large literature. A score of 6 cannot therefore be interpreted as objectively “twice as clinically ready” as a score of 3. It represents a greater number of predefined translational characteristics being satisfied. The TRI therefore measures features associated with translation rather than providing a validated probability of clinical success.

The strongest overall interpretation is therefore an efficacy–translation gap. The efficacy signal is strong: behavioural, histological, and regeneration-related outcomes were generally favourable across the 622 included studies. The translational evidence is considerably less developed. Chronic treatment was investigated in approximately 15.3% of studies, follow-up beyond 12 weeks in 14%, both sexes in 15.9%, aged animals in 12.4%, dose-response in 16.9%, toxicity and scalable manufacturing in 16.1%, and independent replication in only 10.5%.

The result is a marked imbalance. The field has become increasingly successful at demonstrating that scaffolds can improve outcomes under controlled experimental conditions, but far fewer studies assess whether those effects persist under conditions relevant to clinical use. The field has therefore accumulated substantial evidence of efficacy without equivalent evidence of readiness for translation. The preclinical–clinical bridge exists but remains narrow.

4.13 Strengths

Methodological quality was kept separate from regenerative performance. Using SYRCLE independently prevents methodological uncertainty from being incorporated into the regeneration score. A study may report substantial behavioural or histological improvement while providing limited evidence of adequate randomisation, blinding, or allocation concealment. Separating these measures therefore allows favourable findings to be recognised without implying methodological strength.

A further strength is the breadth of the present evidence base. The inclusion of 622 studies allows patterns across a wide range of scaffold materials, architectures, and combination strategies to be examined rather than drawing conclusions from a single scaffold technology. This breadth is particularly relevant when compared with narrower reviews, such as Szymoniuk-et-al., which included only 11 studies of 3D-bioprinted scaffolds[18].

The principal scaffold-class finding also agrees with previous quantitative syntheses. Wang et al. found no significant difference between natural and synthetic scaffolds despite both improving outcomes compared with controls, while Guijarro-Belmar-et-al. found that biomaterial type did not explain substantial heterogeneity in locomotor recovery and axonal regeneration[16].

Taken together, the present descriptive synthesis and previous meta-analyses support the same conclusion: broad scaffold material class is unlikely to be an adequate predictor of therapeutic efficacy. The more important distinction may lie in how scaffolds are designed, combined, and assessed, and whether their apparent efficacy survives the conditions required for translation.

4.14 Limitations

Several limitations should temper interpretation, particularly where descriptive findings are used to compare interventions.

The outcome-scoring system is the main constraint. The 0–2 behavioural scale and composite regeneration measures allowed synthesis of a highly heterogeneous literature but sacrificed quantitative resolution. A score captures the direction and broad magnitude of a finding rather than its precise treatment effect. The behavioural mean of 1.779 therefore cannot be compared numerically with an SMD, mean difference or raw BBB change from conventional meta-analysis.

The behavioural median of 2.0 also indicates a ceiling effect. Because 2 represents the highest category, the score cannot reliably distinguish particularly strong recovery from other favourable findings. The high mean should therefore be interpreted as evidence that favourable outcomes were widespread, rather than evidence of a large average treatment effect.

The TRI presents a similar limitation. Although it provided a consistent way to assess translational characteristics that are often reported separately, it was developed specifically for this review and has not been independently validated. A TRI of 6 cannot therefore be interpreted as objectively twice as translational as a score of 3 or converted into a probability of clinical success. It represents the number of predefined translational characteristics satisfied.

Scaffold classification was necessarily simplified. Categories such as natural, synthetic, composite and electroconductive cannot capture all biologically relevant properties. A lack of class-level differences therefore does not imply that the underlying materials or their properties are equivalent.

Statistical interpretation was further limited by uneven subgroup sizes. The metallic/mineral category contained only two studies and produced a behavioural mean of 2.0, making this estimate particularly unstable. Descriptive differences should therefore not be treated as evidence of superiority where study numbers are exceedingly small.

Substantial heterogeneity also limits interpretation. Species, strain, sex, age, injury model, injury severity, treatment timing, scaffold architecture, and combination therapies varied across studies. A non-significant difference between broad scaffold classes therefore cannot establish biological equivalence; important effect modifiers may simply be distributed unevenly between groups.

Publication bias provides an additional concern. Studies reporting favourable or statistically significant findings may be more likely to reach publication, potentially inflating the apparent prevalence of efficacy. Because this review was predominantly descriptive and did not pool sufficiently homogeneous effect sizes, formal assessment of publication bias was limited.

The review itself also has potential sources of bias. Restriction to English-language publications may have introduced language bias. Screening and extraction were conducted by a single reviewer, with supervisor discussion used to resolve uncertainty. Although necessary given the scale of the project, independent duplicate screening and extraction would reduce the risk of missed studies, inconsistent eligibility decisions, and extraction errors, while permitting inter-reviewer agreement to be quantified.

The review was also not prospectively registered. A predefined methodology was established, but registration was not completed before screening. This reduces transparency compared with a prospectively registered systematic review and limits independent assessment of whether analytical decisions were specified before the findings were known.

Overall, the review is strongest as a descriptive synthesis of patterns, gaps, and relationships across the preclinical scaffold literature. It cannot establish precise comparative treatment effects, demonstrate clinical effectiveness from the TRI, eliminate publication or selection bias, or infer causality from heterogeneous studies. Its conclusions should therefore be interpreted as evidence about the state of the preclinical literature rather than definitive rankings of scaffold efficacy or predictions of clinical success.

4.15 Future Research

The evidence base does not necessarily require another proliferation of scaffold designs; it requires stronger testing of those that already appear promising. Future research should therefore prioritise replication, physiological validation, clinical realism, and controlled comparison of design variables.

Independent replication is an obvious priority. Only 10.5% of studies reported validation by an independent laboratory, making reproducibility one of the clearest weaknesses in the evidence base. A promising intervention should be reproduced outside the laboratory in which it was developed before strong claims are made about efficacy. This is particularly important for complex scaffolds, where fabrication, sterilisation, cell loading, implantation, and postoperative management may influence outcomes.

Electrophysiological assessment warrants similar attention. Only 28 of 622 studies reported electrophysiological outcomes, leaving a substantial gap between evidence of anatomical regeneration and demonstration of functional neural conduction. Behavioural testing captures integrated functional recovery and histology establishes structural change, but neither directly demonstrates that regenerated

or preserved pathways transmit neural signals effectively. Greater use of electrophysiology would therefore help establish whether structural improvements translate into physiological restoration.

Treatment timing also requires deliberate investigation. Only approximately 15.3% of studies examined chronic or delayed treatment, despite the biological differences between acute, subacute, and chronic SCI. Immediate implantation may modify secondary injury effectively but does not necessarily reproduce the circumstances of clinical treatment. Subacute and chronic models should therefore become part of the development of promising interventions rather than an optional later-stage extension. Khodaei-et-al. illustrates why: immediate implantation of a decellularised biological scaffold produced significant motor recovery, whereas implantation after 24 hours did not[20]. Treatment timing should therefore be investigated as an effect-modifying variable.

Durability presents a related problem. Only around 14% of studies followed animals beyond 12 weeks. Short-term improvement does not establish sustained regeneration, particularly for biodegradable scaffolds whose mechanical and biochemical properties change during degradation. Long-term follow-up should therefore determine whether recovery persists after the scaffold has substantially degraded, rather than if early improvement represents durable reconstruction.

The populations studied should also broaden as interventions mature. Both-sex inclusion occurred in only 15.9% of studies and aged animals in approximately 12.4%. Once an intervention has demonstrated sufficient promise, it should be challenged across sex, age, injury severity, and injury model. The predominance of young animals, particularly young male rats, limits the extent to which apparently robust effects can be assumed to generalise across the biological variation encountered in human SCI.

Dose, safety and manufacturing require greater attention alongside efficacy. Only 16.9% of studies examined dose-response relationships and approximately 16.1% assessed toxicity. Demonstrating an effect at one dose does not establish the optimal dose, therapeutic window or point at which adverse effects emerge. Future studies should therefore examine dose-response relationships alongside inflammatory responses, implant tolerance, and degradation-product effects. Manufacturing should likewise establish whether scaffold dimensions, porosity, sterility, and mechanical properties can be reproduced consistently and at clinically relevant scale, particularly for complex composite and biofabricated constructs.

The most important shift may concern what future studies choose to compare. The present class-level findings provide little support for treating natural, synthetic, or composite materials as inherently superior. Research would therefore benefit from identifying functional design principles rather than continually introducing new materials.

Controlled, and where feasible factorial, experiments could address this directly. Rather than comparing unrelated scaffolds that differ simultaneously in material, architecture, cell content and therapeutic cargo, studies could hold the material constant while comparing aligned with randomly orientated architecture, conductive with non-conductive constructs, or alternative degradation rates. Similarly, scaffold-only, cell-only and combination conditions could help distinguish the contribution of each therapeutic component. Such designs would strengthen causal interpretation by identifying which variable is responsible for an observed difference.

The field therefore does not necessarily need more scaffold designs. It needs stronger evidence for those already showing promise: independent replication, clinically realistic treatment windows, durable follow-up, broader biological populations, electrophysiological validation, dose-response analysis, safety testing, and reproducible manufacture. The priority should be to establish not simply whether a scaffold can improve recovery, but which design features produce that effect, whether it survives clinically relevant conditions, and whether it can be reproduced and developed into a viable therapy.

4.15 Scaffold Efficiency Thinking

The present findings argue against treating scaffold efficacy as an intrinsic property of a material. Once implanted into the injured spinal cord, a scaffold acts through the combined influence of material chemistry, architecture, mechanical properties, degradation, biological modification, therapeutic cargo, cellular compatibility, treatment timing, and the host injury environment.

The near-equivalence of the broad scaffold classes illustrates this point. Natural scaffolds had a mean behavioural score of 1.771, compared with 1.780 for synthetic polymers, 1.791 for composites and 1.826 for electroconductive scaffolds. These differences were small, with no significant class-level differences.

This should not be interpreted as evidence that individual scaffold properties are biologically unimportant. Electroconductivity, for example, is being investigated because SCI disrupts neural signalling and electrical properties may influence neuronal activity, axonal growth, and the local cellular environment.

The more appropriate conclusion is that broad material class does not explain enough of the variation in outcome. Scaffolds within the same class can differ in architecture, stiffness, degradation, and biological activity, while materials from different classes may have been engineered to perform similar functions. Thus, the relevant question may be less *what is the scaffold made from?* and more *what functional properties does it provide within the injured spinal cord?*

4.16 Overall Interpretation and Conclusion

Taken together, the findings describe a field that is scientifically productive and capable of producing a substantial regenerative signal, but whose progression from proof of concept towards translational validation remains uneven.

The efficacy signal is difficult to dismiss. Across 622 studies, behavioural outcomes were favourable, with a mean of 1.779, median of 2.0 and SD of 0.415, while total regeneration had a mean of 3.231, median of 3.5 and SD of 0.851. These findings broadly agree with previous systematic reviews and meta-analyses reporting improvements in locomotor recovery and structural regeneration following biomaterial-based interventions in experimental SCI. Krishna-et-al reported improved functional recovery following biomaterial-based approaches, while Guijarro-Belmar-et-al. found significant improvements following biomaterial-based combination strategies[16,17].

Yet the analysis does not identify a clear material winner. Natural, synthetic, composite and electroconductive scaffolds produced similar behavioural scores, with no significant class-level differences in behavioural outcome (p=0.875), histological outcome (p=0.793), total regeneration (p=0.981), or TRI (p=0.777). This closely agrees with Wang et al.'s network meta-analysis, which found no significant difference between natural and synthetic scaffold-assisted cell transplantation (MD −0.35, 95% CI −2.6 to 1.9), despite significant improvements compared with controls[19].

The implication is not that all scaffolds are equivalent. Rather, broad material classification appears too coarse to explain therapeutic performance. Architecture, mechanical properties, degradation, conductivity, biochemical functionalisation, cellular interactions, and therapeutic combinations may be more informative than whether a scaffold is labelled natural, synthetic, or composite. The absence of a class effect therefore shifts the question from *which material is best?* towards *which scaffold properties produce reliable recovery, and under what conditions?*

Combination strategies further support this interpretation. Cells, growth factors, drugs, exosomes, and other adjuncts are frequently incorporated into scaffold systems, reflecting the multiple pathological processes involved in SCI. Previous meta-analysis has demonstrated significant benefits from biomaterial-based combination strategies, while more recent evidence suggests that scaffold-assisted therapies can produce substantial functional effects. However, increasingly complex interventions also make causal attribution more difficult: without appropriate scaffold-only, cell-only and combination controls, the contribution of each component remains uncertain. Biological complexity may therefore increase efficacy while simultaneously making mechanistic interpretation and clinical development more difficult.

The larger weakness appears when the evidence is examined for translational readiness. Only 28 of the 622 studies reported electrophysiological outcomes. Approximately 15.3% investigated chronic or delayed treatment, around 14% followed animals beyond 12 weeks, 15.9% included both sexes and approximately 12.4% used aged animals. Dose-response analysis was reported in 16.9%, toxicity assessment in approximately 16.1%, scalable manufacturing in approximately 16.1%, and independent laboratory validation in only 10.5%.

These figures are more revealing collectively than individually. The problem is not simply the absence of one methodological feature. The evidence base is stronger at demonstrating that an intervention *can* produce an effect than at determining whether that effect is durable, reproducible, physiologically meaningful, safe, and applicable under conditions resembling clinical treatment.

The TRI makes this separation particularly clear. Its mean was 3.22, median 3 and SD 1.657 on a possible 22-point scale. More importantly, TRI was unrelated to behavioural outcome (ρ=-0.010, p=0.814), histological outcome (ρ=0.020, p=0.613) and total regeneration (ρ=-0.009, p=0.832). Stronger regenerative findings therefore did not systematically occur in studies addressing more of the characteristics required for translation. The TRI should not be interpreted as a validated predictor of clinical success, but it provides a useful way of quantifying this separation within the literature.

Methodological reporting presents a related concern. The extensive uncertainty identified by the SYRCLE assessment does not mean that most studies were necessarily at high risk of bias; rather, many reports did not provide sufficient information to judge important safeguards such as randomisation, allocation concealment, blinding, attrition, and statistical analysis. This limits confidence in the evidence and makes replication more difficult. The distinction is important: regenerative performance describes what a study reported, whereas methodological quality determines how confidently that result can be interpreted.

The concentration of the evidence also limits generalisability. Rats accounted for 583 of the 622 studies, approximately 93.7% of the dataset, while only 17 studies involved other species combined. Most studies also used young animals and acute treatment paradigms. Repeated success in a highly controlled rat model demonstrates reproducibility within that model more readily than applicability to the biological variation of human SCI. Similar concerns have been identified by Verstappen-et-al. and Szymoniuk-et-al., who highlighted limitations in animal-model diversity and clinical relevance[18,12].

The present review therefore supports an efficacy–translation gap. Hundreds of experiments have established that scaffold-based interventions can influence recovery after SCI, yet few have subjected those interventions to the additional tests required to establish clinical credibility. This does not mean that scaffold-based tissue engineering has failed. The consistency of favourable findings provides

a strong rationale for continued investigation; the question is whether future work can demonstrate that these effects survive more demanding experimental conditions.

The next stage should consequently prioritise validation rather than simply generating further scaffold designs. Promising interventions should be independently replicated, assessed electrophysiologically, assessed at clinically realistic treatment times and followed for longer periods. Their performance should also be examined across sex, age, and injury models, alongside dose-response, toxicity, and manufacturing assessments. Controlled comparisons of architecture, conductivity, degradation, mechanical properties, and therapeutic combinations would be particularly valuable because they could identify which design features drive recovery rather than attributing efficacy to broad material categories.

The strongest conclusion is therefore not that one scaffold type has emerged as superior. It is that scaffold efficacy appears to depend on the characteristics and conditions of the complete intervention, while translational development has not progressed at the same pace as experimental efficacy. The field has answered *whether scaffolds can work* with considerable confidence; the more subjective questions now concern *why they work, when they work, whether the effect persists, and whether it can be reproduced under clinically relevant conditions*. The next advance may therefore come less from making scaffolds more elaborate than from making the evidence surrounding them harder to dismiss.

5 References

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