Non-Acute Molecular and Imaging Biomarkers for Post-Traumatic Osteoarthritis: A Systematic Review

Introduction

- Post-traumatic osteoarthritis (PTOA) can affect individuals within two years from a trauma injury with an impact on general health, quality of life, and future occupation.
- PTOA is a focus for biomarker research due to the distinct initiating event in a young population with few confounders.
- Previous reviews have synthesized acute (hours-day) and post-acute (days-weeks) phase biomarkers, but there is a need to understand what happens at one year and beyond.

Aim

To describe the utility of serum, synovial fluid and imaging biomarkers and their associations with structural, functional, or symptomatic changes in the chronic phase of PTOA.

Methodology

- A systematic review was performed according to PRISMA guidelines.
- Initial title and abstract screen, and full-text screen were performed by two independent reviewers against pre-determined criteria.

Inclusion Criteria	Exclusion Criteria
• Full text articles, in English, Polish, Danish or Spanish	• Laboratory based, in-vivo or animal studies
• Participants aged 18-45 years old inclusive	• Participants <18 or >45 years old
• Significant injury ≥ 1 year previously	• Significant injury sustained < 1 year ago
• Study involved a 'wet' or 'dry' biomarker	

- Data were extracted and a risk of bias assessment (Newcastle Ottawa Scale, NOS) was performed.
- Extracted data included:
  - Participant numbers and demographic data,
  - Injury type and time from injury,
  - Name type and methodology of biomarkers measured
  - Comparators used in all studies (which included patient-reported outcome measures (PROMS) clinical assessments and imaging.
- Significant differences in study methodology prevented a meta-analysis.
- PROSPERO registration (CRD42022371838)

Results

Figure 1. PRISMA flow chart of systematic review

18 papers: Wet (1-8) Dry (8-18)
Participants: n=1074
Sex: 317 female (102 non-reported)
Age: Early 20s and mid 30s
Time from injury: 1 to 11 years
Anterior Cruciate Ligament (ACL) injury: 17 studies most undergoing ACL reconstruction (ACL-R)
Warfare-associated: 1 study

Molecular biomarkers

- 41 biomarkers measured related to cartilage turnover and inflammation.
- Only five were analysed by more than one study.
- No studies measured urine or used proteomic methods
- Varying associations to different PTOA mechanistic pathway elements or presentations displayed by:

Serum Hyaluronic Acid,
N-telopeptide of Type 1 Collagen,
Cleavage of Type II Collagen,
Tumour Necrosis Factor (TNFα)
Interleukin-10 (IL-10)
Small nucleolar RNA (snoRNA) U38

Synovial Fluid Interleukin-7 (IL-7)
Interleukin-8 (IL-8)
Ghrelin
Pituitary adenylate cyclase-activating polypeptide.

Imaging Markers

- Only MRI have been found in this category.
- Majority of the MRI features have been linked to structural changes including tibial rotation, bone shape and cartilage morphology.
- Several tissue compositional biomarkers utilising T1rho and T2 relaxation times, have been described.

Risk of Bias

Using NOS, one study was unsatisfactory, 11 were satisfactory, and six were good.
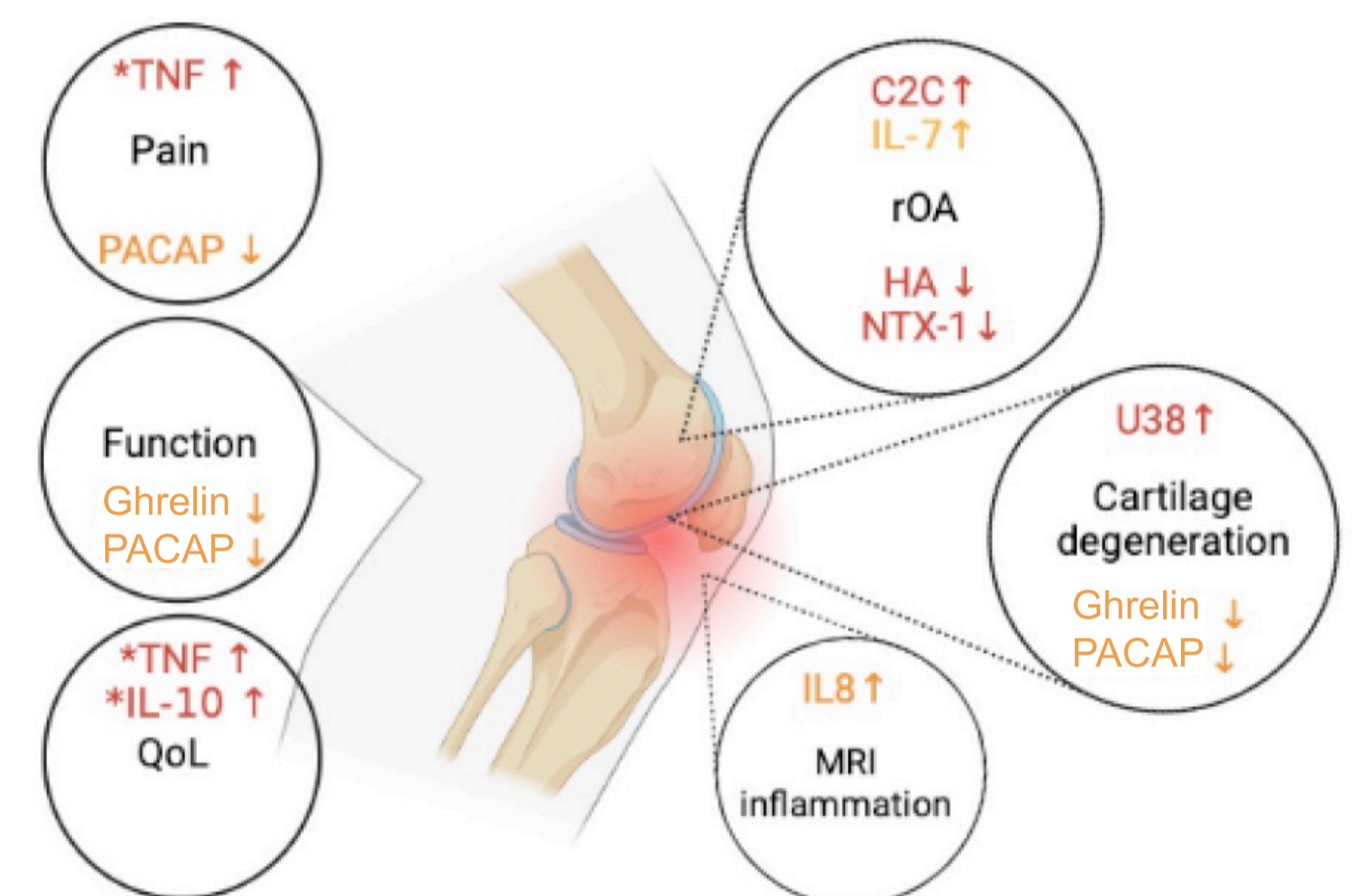
Figure 2. Key findings from molecular biomarkers and their associations to structural, functional, and symptomatic changes at least a year from a significant knee injury.
TNF: Tumour Necrosis Factor, PACAP: pituitary adenylate cyclase-activating polypeptide, IL: Interleukin, C2C: Cleavage of Type II collagen, rOA: radiographic osteoarthritis, HA: Hyaluronic acid, NTX: N-telopeptide of Type 1 Collagen, red signifies serum, yellow signifies synovial fluid

Figure 3. The proposed pathophysiological mechanism of post-traumatic osteoarthritis with key MRI features and their associations a year or more after a significant injury.
MRI: Magnetic Resonance Imaging, SSM: Statistical Shape Modelling, TT: Tibial translation, TR: Tibial rotation.

Figures created in BioRender.

References

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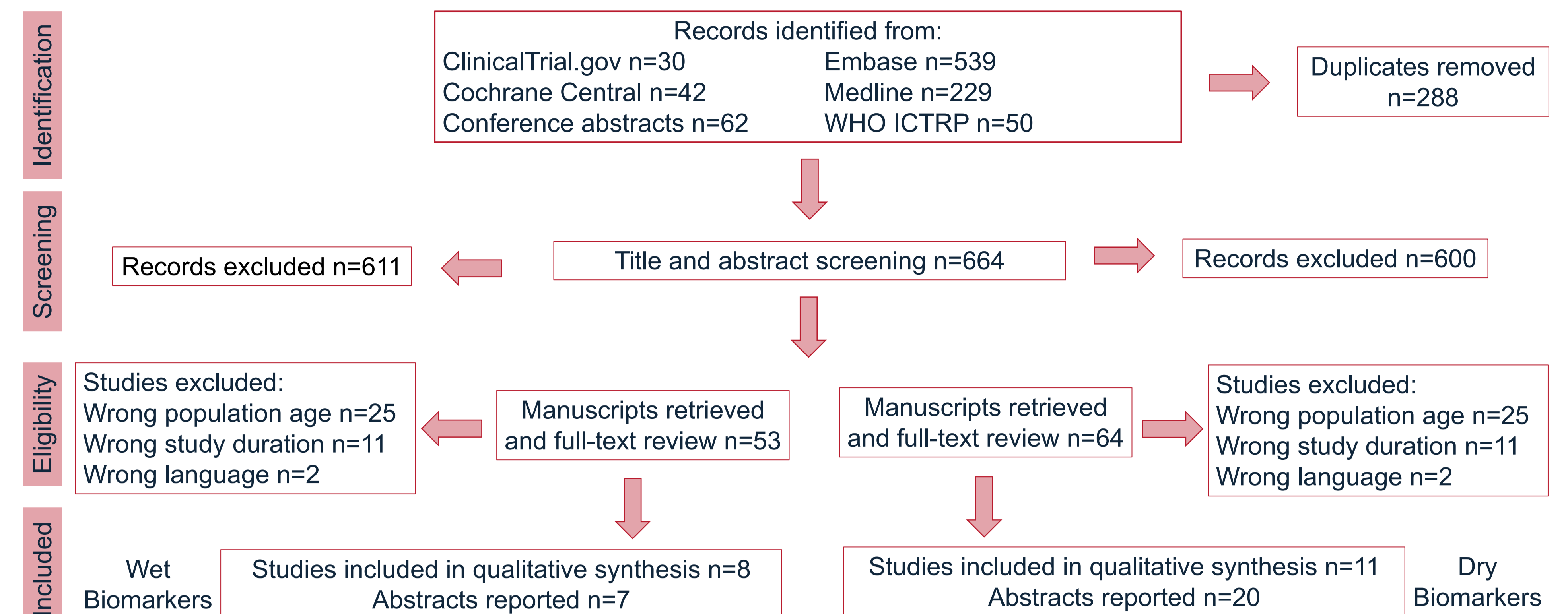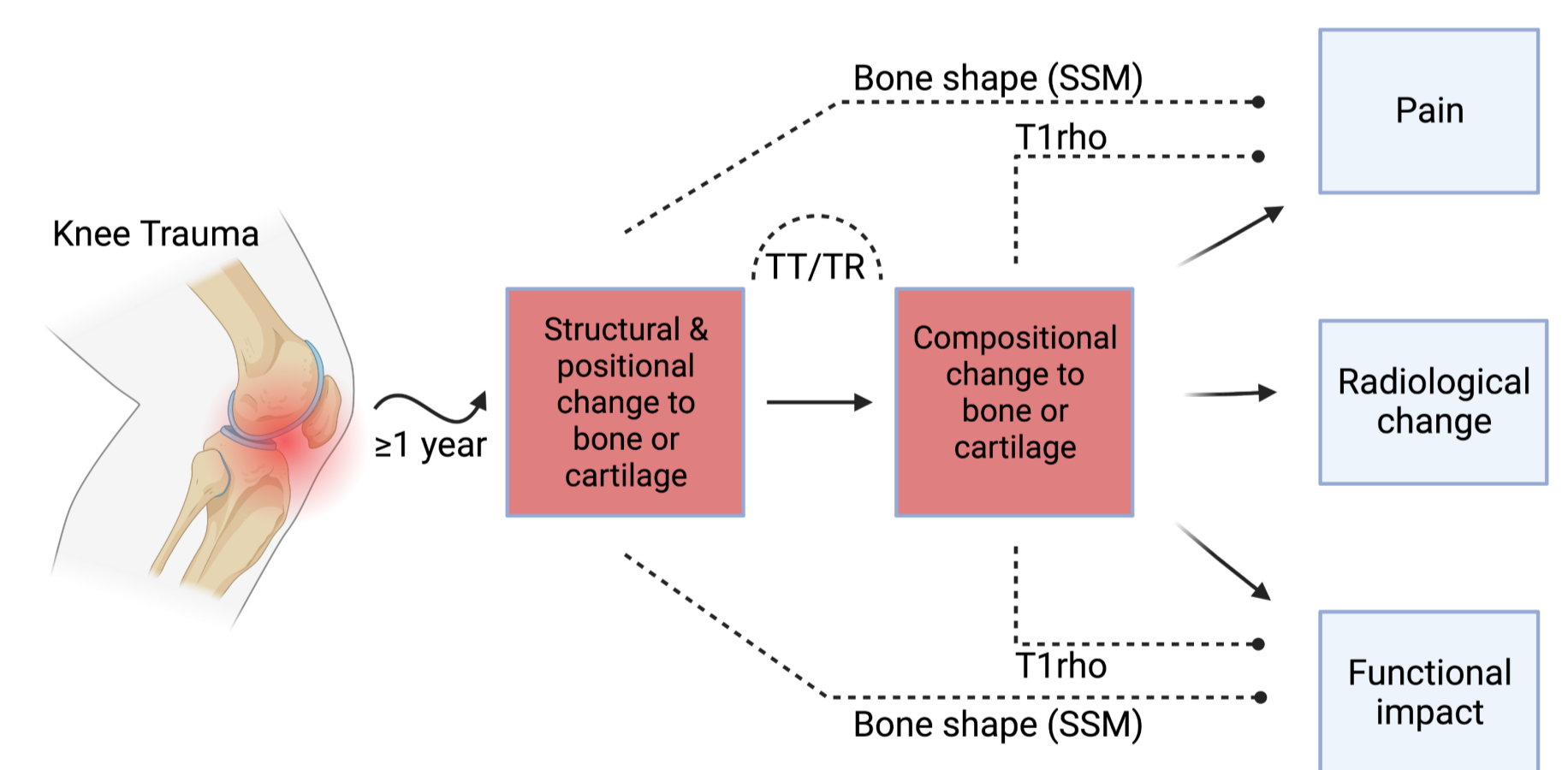
Conclusion

- Wet and dry biomarkers associated with bone and cartilage composition as well as inflammatory response have been highlighted in this review.
- MRI biomarkers suggest a strong association with structural changes, with joint position, bone, and cartilage shape followed by compositional changes in the cartilage being linked with either PROMs, radiographic progression, and pain.

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