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REVIEW

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High-precision in vivo tracking of stem cells using carbon-14 labeling: a novel quantitative approach for assessing therapeutic efficacy and safety

Sungmin Kim[1], Mingu Ryu[2], Hee-Sick Youn[2], Yun-Gwi Park[2] and Sung-Hwan Moon[2*]

Abstract

Background Accurate long-term tracking of transplanted stem cells is essential for evaluating therapeutic efficacy, biodistribution, and safety in regenerative medicine. Conventional imaging and molecular tracing methods often lack the sensitivity or temporal stability required for quantifying small residual cell populations over extended periods. Carbon-14 (C-14), a long-lived radioactive isotope, offers a unique opportunity to overcome these limitations by enabling durable and quantitative labeling of stem cells.

Main body C-14 labeling provides an inheritable molecular marker that is stably incorporated into nucleic acids and other macromolecules, permitting attomole-level detection using accelerator mass spectrometry (AMS). This analytical sensitivity enables reliable quantification of fewer than 100 transplanted cells within complex host tissues—an order of magnitude beyond the detection limits of polymerase chain reaction (PCR) and other conventional assays. Through AMS-based analysis of time-resolved tissue samples, C-14 tracing supports precise assessment of cell survival, migration, engraftment, and long-term persistence. The approach further allows the identification of adverse outcomes such as ectopic engraftment, uncontrolled proliferation, or tumorigenicity by detecting abnormal expansion or mislocalization of labeled cell populations. Collectively, C-14-based tracking provides both quantitative accuracy and temporal resolution suitable for rigorous preclinical evaluation of stem cell therapies.

Conclusion C-14 tracing represents a powerful analytical platform capable of transforming cell tracking strategies in regenerative medicine. Its unparalleled sensitivity and long-term detection capability offer clear advantages for studying stem cell fate, optimizing therapeutic protocols, and strengthening safety assessments. Continued methodological refinement and broader standardization will be crucial for translating this technology into wider preclinical and clinical use.

Keywords Carbon-14, Stem cells, In vivo tracking, Biodistribution, Tumorigenicity, Regenerative medicine, Radiotracer, Accelerator mass spectrometry

1 Background

Stem cell therapy represents a transformative development in regenerative medicine by providing potential treatments for degenerative, autoimmune, and ischemic diseases [1, 2]. However, clinical translation is limited by the difficulty of monitoring transplanted cells in vivo [2]. Accurate evaluation of efficacy and safety requires

*Correspondence:
Sung-Hwan Moon
moonsh@cau.ac.kr
[1] University of Bristol, University Walk, Bristol, United Kingdom
[2] Chung-Ang University, Anseong, Korea, Republic of

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tracking cell survival, engraftment, migration, differentiation, and potential adverse effects such as tumor formation [3].

The main tracking methods currently available for monitoring stem cells, including fluorescence labeling, magnetic resonance imaging (MRI) techniques, positron emission tomography (PET) scans, and polymerase chain reaction (PCR)-based genetic tagging, are limited by short signal duration, low sensitivity, and measurement inaccuracies [4, 5]. Current tracking methods cannot provide long-term quantitative assessments of transplanted stem cell behavior, especially at low cell densities or in unexpected locations [6].

Radioactive isotopes such as Carbon-14 (C-14) offer a promising solution to these limitations in stem cell tracking [7]. The beta-emitting isotope C-14 occurs naturally and has a half-life of approximately 5730 years which allows scientists to detect labeled cells over extremely long periods without experiencing signal decay throughout biologically meaningful durations [8]. Once C-14 becomes a part of cellular biomolecules, such as DNA, RNA, proteins, or lipids, it creates a permanent marker that remains with the cell and its progeny throughout its existence [9].

Accelerator mass spectrometry (AMS) enables the attomolar detection of C-14, allowing for the quantification of fewer than 100 cells in complex biological samples—levels beyond the reach of conventional imaging or molecular methods [10]. This technique enables researchers to quantify fewer than 100 cells from intricate biological samples that conventional imaging or molecular methodologies cannot measure [11]. C-14 emits low-energy beta radiation has minimal biological effects, which makes it appropriate for animal longitudinal studies and potentially safe for human clinical trials if strict safety measures are followed [9].

This review explores the integration of C-14 labeling with AMS detection in stem cell research. We discuss its biophysical and methodological aspects and highlight its advantages over current tracking methods. Its applications include quantifying engraftment, mapping biodistribution, and evaluating therapeutic outcomes, including safety concerns such as off-target effects and tumor formation. By enabling precise long-term tracking, C-14-based methods can deepen our understanding of regenerative therapies and facilitate their safe clinical translation.

2 Methodology for C-14 labeling and detection

Accurate and consistently repeatable protocols that prioritize safety during labeling and detection operations are essential for effective stem cell tracking using C-14 [9]. This section details the methodological framework required to implement C-14-based tracing in stem cell research, focusing on three key components (Fig. 1). The study of C-14 stem cell tracking involves protocols for labeling cells, detection methods using AMS, and radiation safety dosimetry strategies [7, 10].

Schematic representation of the complete ^{14}C-based AMS workflow for stem cell tracking. Stem cells are labeled with ^{14}C-labeled compounds, such as thymidine, uridine, or glucose, which become incorporated

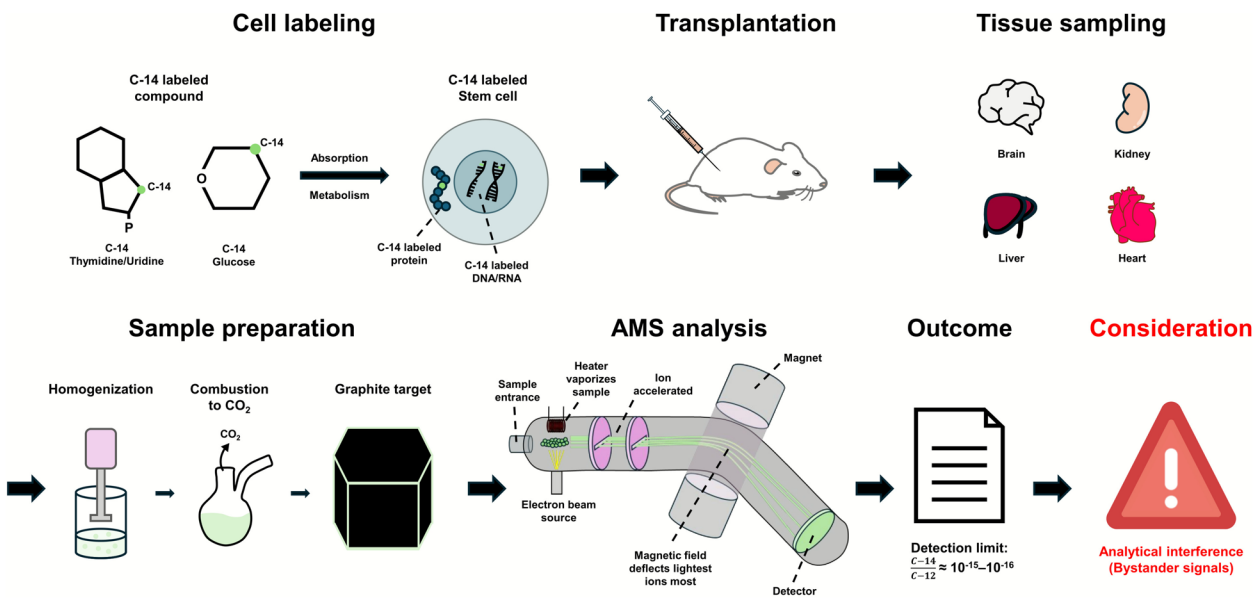


Fig. 1 Workflow of carbon-14 (^{14}C)-based stem cell tracking using accelerator mass spectrometry (AMS)

into cellular macromolecules (DNA, RNA, or proteins). Following in vivo transplantation, tissue samples are collected from multiple organs at defined time points and undergo standardized preparation steps, including homogenization, combustion to CO_2, and conversion to graphite targets, prior to AMS analysis. The AMS system separates carbon isotopes (^{12}C, ^{13}C, and ^{14}C) by mass-to-charge ratio, with signals quantified at attomole sensitivity (detection limit $^{14}C/^{12}C \approx 10^{-15}$–$10^{-16}$).

2.1 C-14 labeling protocols

Labeling stem cells with C-14 involves inserting radioactive molecules into specific cellular macromolecules such as DNA to produce a permanent and inheritable marker. C-14-labeled thymidine remains the primary labeling agent because it directly integrates as a nucleoside into DNA during the S-phase of cell division. Researchers can use various labeling compounds, including C-14-uridine for RNA analysis and C-14-glucose to study metabolic pathways, while C-14-leucine or C-14-lysine helps assess protein synthesis to target distinct cellular compartments or functions according to research objectives [12].

Stem cells such as mesenchymal stem cells, induced pluripotent stem cells (iPSCs), and neural stem cells are cultured in defined growth media containing a known concentration of C-14-labeled compound during the initial step of the labeling process [7, 13]. The exposure duration depends on the target labeling depth and the cell proliferation rate. DNA labeling method with C-14-thymidine requires cells to be incubated for 24–72 h to achieve maximum incorporation into dividing cells [14]. Optimization of C-14 labeling conditions is critical to achieving high incorporation efficiency while preserving cell viability. Typical labeling concentrations range from 0.1 to 1.0 μCi/mL of C-14-thymidine, depending on the proliferation kinetics of the target cell population. Excessive isotope concentration can impair metabolic activity; therefore, pilot assays should be conducted to determine the lowest effective activity that produces uniform labeling without cytotoxicity [15]. The incubation period (24–72 h) should be adjusted according to the doubling time of the specific stem cell type to ensure sufficient DNA incorporation during the S-phase. Medium composition also influences labeling efficiency; maintaining a low background carbon source and consistent serum content minimizes isotope dilution and metabolic interference. Following incubation, small aliquots can be analyzed by liquid scintillation counting or AMS microsampling to verify labeling uniformity across the population. Optimization should also include post-labeling viability and differentiation tests, confirming that C-14 incorporation does not alter proliferation, surface marker expression, or lineage potential [14, 15].

After incubation, the extracellular radioactive substances and loosely associated radioactive materials were removed by thorough washing to eliminate residual isotopes. The critical step in quantifying C-14 incorporation requires scintillation counting of aliquots or preliminary AMS assessment to check the labeling efficiency and consistency throughout the cell population [16, 17]. Downstream biodistribution studies require uniform labeling to ensure that the data remain interpretable.

Validation of labeling efficiency is an essential step before proceeding to in vivo studies. Typically, a small representative aliquot of the labeled cell population is analyzed to confirm both incorporation efficiency and homogeneity. Liquid scintillation counting (LSC) can provide a rapid preliminary estimate of total radioactivity per cell, whereas AMS-based micro-sampling offers absolute quantification of the $^{14}C/^{12}C$ ratio at attomole sensitivity [7, 15]. For accuracy, results from these quantitative assays are normalized to cell number and compared with unlabeled controls to exclude the nonspecific adsorption of the isotope. In addition, autoradiographic imaging or phosphor plate exposure can be used to visualize the uniformity of label distribution among cells, confirming the absence of "hot" or "cold" subpopulations [15, 18]. A coefficient of variation below 10% in $^{14}C/^{12}C$ ratios across replicate measurements is generally accepted as a benchmark for uniform labeling. Finally, post-labeling viability and proliferation assays (e.g., trypan blue exclusion, MTT, EdU incorporation) are performed to ensure that the labeling procedure does not alter cellular function or induce cytotoxicity [15, 19].

The labeling process must avoid damaging the biological functions of the cells to maintain their therapeutic potential. Labeled cells must undergo thorough post-labeling tests like flow cytometry for surface markers, quantitative PCR (qPCR) for pluripotency and lineage-specific genes, and in vitro differentiation protocols to ensure they maintain the same phenotypic and functional characteristics as unlabeled cells [15, 20].

Biosafety precautions require consistent enforcement of the labeling process. Research involving C-14 compounds must be conducted in licensed radiological facilities equipped with shielding, contamination control, and approved waste disposal systems, in compliance with institutional and national safety standards.

Although C-14 labeling introduces minimal radiation, the incorporation of radiocarbon-labeled nucleotides could theoretically alter cell viability or pluripotency if labeling conditions are excessive. Empirical studies, however, have shown that low specific activity labeling (typically ≤ 0.1 μCi per 10^6 cells) does not affect stem cell proliferation, morphology, or differentiation capacity when compared with unlabeled controls [9, 20,

21]. Pluripotency markers such as *OCT4*, *SOX2*, and *NANOG* remain stably expressed after C-14-thymidine incorporation, and subsequent lineage-specific differentiation assays into osteogenic, adipogenic, or neuronal lineages confirm preserved developmental potential [7]. Moreover, AMS-based microtracer studies involving human or animal cells have reported no measurable cytotoxic, genotoxic, or metabolic alterations at tracer-level labeling intensities [22, 23]. These findings collectively support that C-14 labeling—when performed under microtracer-level activity and with adequate washing to remove unincorporated isotopes—does not compromise stem cell potency or viability.

2.2 Detection via AMS

AMS technology achieves attomolar sensitivity for isotope detection, corresponding to the detection of radiocarbon amounts equivalent to approximately 50–100 labeled cells under optimized analytical conditions. Calibration curves relating $^{14}C/^{12}C$ ratios to known cell numbers have been established in relevant biological matrices, demonstrating linearity across this range ($R^2 > 0.999$) with low analytical imprecision (< 1% CV). In addition, unlabeled control samples showed no measurable ^{14}C signal above background, confirming negligible false-positive detection. Such ultra-trace sensitivity has been demonstrated in biomedical AMS studies detecting 10^{-15}–10^{-18} mol ^{14}C in biological matrices [7, 24, 25]. These results substantiate the feasibility of quantifying small labeled cell populations in complex tissues using AMS [24]. Unlike scintillation counting and autoradiography, AMS does not require high radiation energy for detection and operates without overlapping background noise, which allows precise quantitative analysis [26, 27].

The detection process is initiated by gathering tissue samples from specific target areas, such as injured or diseased organs, along with other nonspecific body regions to assess biodistribution. The samples were thoroughly homogenized before isolating the carbon through combustion to CO2 and then transforming it into graphite. AMS processes graphite to separate individual carbon isotopes based on their mass-to-charge ratio and then counts each isotope independently [28].

During AMS analysis, negatively charged carbon ions (C^-) are generated from the graphite target by cesium sputtering within the ion source and accelerated to several MeV through a tandem accelerator. Molecular interferences such as $^{13}CH_2^-$ and $^{12}CH_3^-$ are removed as the ions pass through a stripper stage, ensuring that only atomic ions reach the high-energy detector [29]. The $^{14}C/^{12}C$ ratio is quantified using gas ionization or silicon detectors, and measurements are normalized against standards such as NIST SRM 4990C (Oxalic Acid II) and ANU sucrose. Analytical precision typically reaches ± 0.3% for isotope ratios, corresponding to an absolute detection limit near 10^{-18} mol ^{14}C [30, 31].

AMS provides exceptional precision in measuring the C-14 to C-12 ratio, resulting in the exact quantification of labeled cells in each tissue sample [19]. Subsequent methodological advances have expanded AMS applications from radiocarbon dating to biomedical quantification, demonstrating reliable attomole-level sensitivity and isotope ratio precision across diverse biological matrices [23].

The exceptional sensitivity of AMS forms the analytical foundation for time-resolved biological tracking, as discussed in Sect. 3. By providing absolute isotope quantitation, AMS enables subsequent applications in stem cell fate mapping, biodistribution, and safety analysis. The exceptional sensitivity of this method tracks residual cell populations over extended periods after therapeutic effects occur and allows longitudinal studies without facing the signal degradation problems typical of alternative techniques [32].

Another analytical limitation concerns potential interference from endogenous or dietary ^{14}C naturally present in biological samples ($\sim 1.2 \times 10^{-12}$ mol ^{14}C per mol C). Although AMS discriminates labeled material by its elevated $^{14}C/^{12}C$ ratio, rigorous background correction and the inclusion of unlabeled biological controls are required to achieve quantitative accuracy. Standard practice involves subtracting natural isotopic abundance and applying calibration with modern carbon standards to ensure that signals exceeding natural background ($\approx 100 \times 10^{-12}$ mol ^{14}C per mol C) represent true tracer incorporation [23].

To ensure analytical accuracy and inter-laboratory reproducibility, AMS measurements are routinely calibrated using internationally recognized standards such as NIST SRM 4990C (Oxalic Acid II) and ANU sucrose as modern carbon references [33, 34]. Each batch of biological samples is analyzed together with blank and secondary standards to correct for isotopic fractionation and machine drift. Internal normalization to $^{13}C/^{12}C$ ratios further compensates for ion source instability, while routine cross-checks against long-lived standards such as IAEA-C6 and FIRI-C monitor long-term instrument performance [35, 36]. Quality assurance protocols also include periodic remeasurement of archived reference materials, background subtraction using unlabeled control tissues, and inter-facility cross-calibration exercises coordinated through BioAMS networks [37]. These procedures collectively establish traceable accuracy at the sub-percent level, providing the analytical reliability necessary for quantitative biomedical applications.

AMS operates without optical or radiographic imaging capabilities which enables its use in evaluating tissues that lack transparency and possess anatomical intricacy while extending its utility to multiple organ systems and different model organisms. AMS is essential for preclinical stem cell therapy validation because of its methodological stability [38].

Recent analyses have highlighted that despite major advances in sensitivity and biosafety, AMS remains constrained by high operational costs, limited facility availability, and the need for specialized technical expertise [39, 40]. These factors currently restrict its widespread adoption beyond dedicated biomedical AMS centers.

2.3 Label stability and interpretive limitations of ^{14}C-AMS tracking

A critical parameter for accurate radiocarbon-based cell tracking is the stability of ^{14}C-thymidine once incorporated into cellular DNA. Studies using post-mitotic human neurons have demonstrated remarkable long-term label retention, confirming that ^{14}C-labeled DNA can persist for decades without measurable degradation [41, 42]. However, in proliferative stem or progenitor populations, the ^{14}C signal is predictably diluted by half with each cell division, following binary kinetics. Comparisons with thymidine analogs such as BrdU or EdU have shown that up to several cell cycles can be resolved above AMS background under optimized labeling conditions [23].

Additional factors, including DNA repair–mediated nucleotide replacement, nucleoside recycling from apoptotic cells, and asymmetric DNA segregation, can influence apparent turnover estimates [43]. Although these phenomena have been recognized in isotopic turnover studies, their quantitative impact under AMS detection remains insufficiently characterized, particularly in distinguishing bystander ^{14}C signal arising from free nucleosides released by dying cells from true intact-cell migration. Future research combining AMS quantification with cell-cycle markers, live imaging, and experimental cell-death controls will be essential to define the detection limits and improve interpretive accuracy in proliferating stem cell systems [44–46].

Experimental validation of C-14–based AMS tracing has been demonstrated across multiple preclinical and human studies. Early proof-of-concept work by Lappin and Garner (2003) quantified ^{14}C-labeled human lymphocytes in rodents and confirmed label stability and recoverability in peripheral tissues for more than six months using AMS analysis [9]. Minamimoto et al. (2008) further verified this sensitivity in human microtracer trials, showing reliable detection of ^{14}C-labeled compounds at attomole levels with no measurable biological or genotoxic effects [22]. More recent experimental work has demonstrated the feasibility of AMS-based ^{14}C-thymidine cell tracking in stem cell models. Notably, adipose-derived mesenchymal stem cells labeled with ^{14}C-thymidine were quantified in multiple organs at single-cell sensitivity using ultra-sensitive AMS, which achieved a linear calibration curve ($R^2 = 0.9997$) and < 1% analytical imprecision from over 50,000 ion counts [7]. In that study, unlabeled control samples showed no detectable ^{14}C signal above background, confirming minimal false-positive detection. AMS has also been applied to quantify the engraftment of hESC-derived endothelial cells in ischemic models [38, 47]. These studies provide direct experimental validation that AMS can deliver absolute quantitation of cellular biodistribution and persistence in vivo, although comparable, high-quality AMS reports for hematopoietic stem cells remain limited in the literature and require further investigation [7]. Together, these experimental validations support the robustness, sensitivity, and biosafety of C-14 labeling as a long-term cell tracking strategy.

Although these studies collectively validate the feasibility and sensitivity of AMS-based ^{14}C tracing, most published investigations remain at the proof-of-concept stage. Existing work has primarily focused on demonstrating detectability, labeling stability, and safety within isolated models rather than performing statistically powered or comparative analyses. Systematic, multi-center validation studies, particularly those benchmarking AMS against conventional imaging-based tracking methods, are still limited in the literature. Addressing this gap is essential to strengthen the translational credibility of AMS-based cell tracking approaches.

Despite these encouraging validations, there remains a lack of systematic benchmarking of ^{14}C-AMS against other established tracking modalities such as PET, MRI, and fluorescence-based imaging. Most published studies have focused on demonstrating detection sensitivity or long-term label stability within isolated models, without using standardized experimental metrics that enable direct performance comparison. The importance of rigorous cross-platform evaluation has been widely recognized in reviews addressing imaging and radiotracer quantification standards [9, 48]. The need for harmonized study designs to assess reproducibility and analytical precision across tracking systems has also been highlighted [49]. Establishing such standardized comparative frameworks will be critical for validating the quantitative and translational advantages of AMS-based cell tracking [9].

Although AMS offers distinct advantages in sensitivity and temporal stability, previous studies have seldom reported standardized quantitative comparisons with existing tracking methods. Published metrics indicate

that AMS achieves isotopic quantification down to 10^{-18} mol ^{14}C (≈ 50 cells), whereas PET and MRI typically detect tracer concentrations in the 10^{-9}–10^{-12} mol range, corresponding to 10^{6}–10^{9} cells depending on the tracer and tissue depth [30, 50, 51]. This difference highlights that AMS provides 6–9 orders of magnitude higher molecular sensitivity, albeit at the expense of real-time imaging capability and throughput. Incorporating such quantitative benchmarks is essential to objectively contextualize the role of AMS relative to conventional imaging-based tracking.

A further methodological limitation lies in the lack of standardized analytical protocols across AMS facilities. Variability in graphite preparation, ion source calibration, and isotope ratio normalization can introduce inter-laboratory discrepancies of up to 10%. International working groups have emphasized the need for harmonized reference materials and cross-calibration exercises to ensure reproducibility in biomedical AMS studies [30, 31]. Establishing shared quality-assurance frameworks will be essential for translating AMS quantitation into regulated clinical applications.

A further aspect of reproducibility concerns inter-laboratory consistency in AMS measurements. Comparative analyses among major AMS facilities, including CAMS (USA), Leibniz-Laboratory (Germany), and LLNL (USA), have shown deviations of up to 5–10% in $^{14}C/^{12}C$ ratios depending on graphite preparation methods and ion source conditions [52]. To address this issue, international working groups have implemented cross-calibration and round-robin exercises using certified reference standards to harmonize analytical performance across laboratories. These collaborative inter-comparison efforts have successfully reduced analytical variance to within ± 2%, establishing reproducibility levels suitable for regulatory and clinical research translation.

The importance of facility-level best practices and instrument-operating standards has been emphasized in instrumentation reports and facility descriptions (e.g., operation of small BioAMS spectrometers and liquid-sample interfaces), which document practical sources of variability and routes for harmonization. Examples include detailed method and operations descriptions from major biomedical AMS centers [53, 54].

Together, these methodological advances establish AMS as a uniquely quantitative platform for tracking stem cell fate in vivo. The ability to detect attomolar levels of ^{14}C within complex tissues enables the precise assessment of cell survival, migration, and differentiation. The following section outlines how this analytical framework has been applied to address key questions in stem cell therapy, including biodistribution, efficacy, and safety evaluation.

3 Applications in stem cell research using C-14 labeling

C-14 labeling enables researchers to accurately monitor stem cell activity over extended periods by monitoring survival rates, proliferation patterns, and differentiation processes [55]. This method excels in delivering quantitative data over long durations, which is essential for stem cell therapies because tracking transplanted cell fate determines therapeutic success and safety [15, 56]. The application of C-14 tracing in monitoring stem cell behavior addresses important safety issues, such as tumor development and unwanted tissue formation, while minimizing off-target effects to enhance the effectiveness of stem cell therapy. In this section, we explore the key applications of C-14 in stem cell research: C-14 tracing provides quantitative cell fate tracking along with biodistribution assessment and enables the evaluation of therapeutic efficacy as well as safety monitoring.

3.1 Quantitative tracking of cell fate

Building upon the aforementioned AMS detection principles, C-14 labeling allows researchers to quantitatively monitor stem cell behavior over extended periods, providing crucial insight into survival, proliferation, differentiation, and tissue integration. Extended cell tracking facilitated by C-14 (long half-life of 5730 years) enables researchers to study stem cell behaviors that other short-lived tracers fail to capture [15].

The C-14 labeling technique works through the metabolic absorption of the isotope into nucleotides including ^{14}C-thymidine for DNA synthesis and ^{14}C-glucose for cellular metabolism [57]. The radioactive marker introduced through incorporation remained stable and permitted long-term detection during cell division and differentiation into multiple cell types [58]. The C-14 label transferred from stem cells to daughter cells during cell division enables scientists to track cell populations continuously over extended periods spanning weeks to years unlike alternative markers [59].

Extended monitoring of cells enables scientists to study fundamental processes such as stem cell self-renewal, desired lineage differentiation, and target tissue integration [60, 61]. C-14 labeling enables scientists to track the survival duration and integration efficiency of transplanted stem cells into damaged tissues while assessing their contribution to functional recovery [7, 15]. Evaluating the therapeutic potential of stem cells and their long-term regenerative benefits is essential.

In addition to tracking differentiation processes, C-14 labeling can also serve as a sensitive approach to monitor potential tumorigenic behavior in transplanted stem cells. The specific mechanisms and safety frameworks

for tumorigenicity monitoring are discussed in detail in Sect. 3.4 (Safety Monitoring and Tumorigenicity Analysis).

C-14 labeling remains active over extended periods, which allows it to reveal initial malignant changes such as unchecked cellular growth and abnormal tissue development before tumors become detectable [3]. Early detection capabilities play a vital role in reducing potential risks from stem cell therapies while maintaining the safety of treatments over the long term. Researchers prevent cancer development through early interventions enabled by monitoring abnormal cell growth and tumorigenic alterations during experiments [62, 63].

3.2 Assessment of Biodistribution and Homing

The use of C-14 labeling provides a precise distribution mapping of stem cells after transplantation into the host organism [64]. A major obstacle in stem cell therapy involves directing cells to migrate and integrate properly into the target tissue while avoiding unintended side effects, such as ectopic tissue development or cell clustering in non-target organs [65, 66]. Scientists can determine stem cell homing efficiency and tissue migration patterns using C-14 tracing techniques.

Stem cells must effectively navigate to injury or disease sites during homing to ensure successful regenerative therapy outcomes [67–69]. The use of C-14 enables researchers to accurately monitor how labeled stem cells navigate from their injection site to multiple organs and tissues [11]. Scientists can ascertain the migration efficiency of stem cells to target areas such as the heart or brain by analyzing the distribution patterns of C-14-labeled cells throughout multiple tissues over time [15]. By mapping the movement of cells, researchers can detect which organs or tissues receive unintended cell migration and evaluate the potential safety risks [3].

When stem cells intended for neural regeneration migrate to unintended sites such as the liver or lungs, they may cause adverse health effects such as fibrosis or tumor formation [70]. C-14 tracing provides an effective instrument for evaluating these potential risks because it allows real-time monitoring of cell distribution patterns. In clinical applications, stem cell therapies require the highest levels of safety and specificity which C-14 tracing can achieve [71].

The ability to track cell distribution using C-14 helps researchers determine the target specificity of the stem cell therapies [55]. The prevention of stem cell migration to unintended tissues by maintaining them localized at the target site is essential to reduce off-target effects [72, 73]. Studying the distribution of C-14-labeled stem cells throughout the body enables researchers to refine delivery methods and target tissue conditions, thereby enhance accuracy and minimize side effects [7, 70].

3.3 Evaluating therapeutic efficacy

Stem cell therapy effectiveness depends on transplanted cells achieving successful engraftment and long-term survival [74, 75]. Through C-14 labeling researchers have gained quantitative insights into stem cell treatments by monitoring viable cell counts in target tissues over time. The number of residual cells initially increased within the first 12 h after transplantation, followed by a marked decrease at up to 48 h, and a subsequent increase at 168 h, indicating partial cell recovery or redistribution within host tissues (Fig. 2) [7]. The correlation between cell dosage and therapeutic outcomes requires further understanding because it serves as a key element for optimizing doses in clinical applications [76, 77].

The number of residual C-14 thymidine-labeled cells detected in the liver, heart, and brain at different time points post-injection, quantified using accelerator mass spectrometry (AMS). Data are presented as mean ± SD (n = 3) and adapted from Oh et al. (2021). Residual cell numbers increased at 12 h, declined up to 48 h, and showed a secondary increase at 168 h after transplantation. Data reproduced and reanalyzed from Oh et al. (2021).

A primary challenge in stem cell therapy is identifying the perfect cell quantity required to attain the expected therapeutic outcome [78, 79]. Through C-14 tracking researchers can accurately measure transplanted stem cell populations in tissues, which helps understand their relationship with functional recovery [80]. Determining the correct number of stem cells required for transplantation in cardiac repair therapy will help clinicians make informed decisions [78].

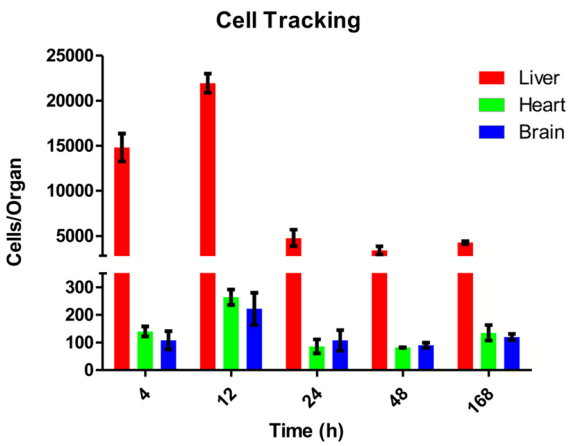


Fig. 2 Quantitative AMS-based tracking of Carbon-14 (C-14) labeled cells in major organs

The long-term benefits of stem cell therapies can be evaluated by measuring cell survival and persistence [81, 82]. The duration of stem cell viability and function within tissues can be measurable using C-14 tracing which provides evidence regarding therapeutic longevity [83]. Long-term monitoring procedures identify whether transplanted cells maintain their regenerative function or become less effective over time, while producing essential data to improve treatment methods [84, 85].

The precise measurement capabilities of C-14 labeling enable healthcare providers to craft individualized treatment plans using optimized cell dosages. When researchers understand how cell dosage is related to therapeutic results and long-term survival, they can establish the optimal stem cell dosage to achieve peak therapeutic effects [79]. Clinical trials have found this approach to be particularly useful because it adjusts for patient variability to deliver the optimal dose based on the condition of the patient [86, 87].

3.4 Safety monitoring and tumorigenicity analysis

Tumorigenicity monitoring is a critical aspect of stem cell therapy safety evaluation. Pluripotent stem cells, including iPSCs and ESCs, retain the ability to differentiate into multiple lineages, which inherently carries a risk of teratoma and other uncontrolled proliferative outcomes [88]. C-14-based tracking provides a reliable and quantitative means of identifying these abnormal events by measuring persistent or ectopic proliferation and migration of labeled cells across tissues [15, 89]. By continuously monitoring transplanted stem cells over extended periods, this approach enables the early detection of unwanted growth, thereby strengthening the biosafety assessment of cell therapy products.

In previously reported teratoma monitoring studies, the observation period and sampling intervals were typically designed to capture both early engraftment and long-term persistence phases, generally extending up to 90 days post-transplantation. The statistical evaluation of tumorigenic potential in these models was based on incidence rates rather than survival analysis, as no teratoma or abnormal proliferation was observed in the labeled cell groups.

Moreover, it was confirmed that C-14 labeling did not alter the intrinsic characteristics of the cells, as in vitro analyses showed no significant changes in cell characteristics (proliferation rate, expression of specific markers, and cell cycle) after labeling. Furthermore, during the 90-day in vivo tracking period, no abnormal cell persistence or proliferative expansion was detected in the transplanted tissue, indicating that the labeled cells maintained physiological stability without evidence of adverse growth behavior [38].

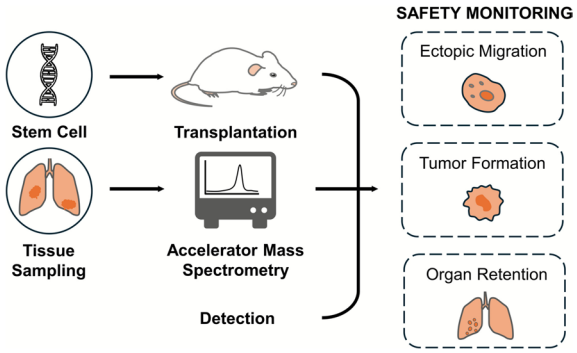


Fig. 3 Safety monitoring framework for stem cell therapy using carbon-14 (C-14) labeling and accelerator mass spectrometry (AMS)

C-14 tracing sensitively detects abnormal stem cell proliferation or migration that may lead to tumor formation (Fig. 3) [7]. Monitoring transplanted cells over extended periods provides essential safety surveillance, particularly for pluripotent stem cells such as iPSCs and ESCs, which inherently carry a risk of teratoma formation [90, 91].

Workflow diagram illustrating the use of C-14 labeling and AMS for safety assessment in stem cell therapies. Labeled stem cells are transplanted into animal models and later assessed through tissue sampling and AMS analysis to detect ectopic cell migration, tumor formation, or unwanted organ retention. This process supports early identification of tumorigenic risks and improves safety monitoring during preclinical and clinical development.

The extended half-life of C-14 together with its cellular persistence make it an ideal tool for tracking tumorigenic risks during stem cell transplantation [92]. The study of C-14-labeled cells proliferation and migration behavior enables researchers to detect abnormal cell growth patterns that signal potential teratoma formation and other tumor types [93, 94]. The ability to detect early warning signs is a vital component of safety of the stem cell therapy by providing opportunities for swift intervention to halt malignancy formation [56, 95].

C-14 tracing technology enables the ongoing observation of transplanted stem cells in clinical therapies to promptly detect and manage possible tumor formation or ectopic tissue development [96]. The unique characteristics of iPSCs and ESCs make this process critical, because they can form several cell types that may lead to tumor development. C-14 labeling provides a dependable safety assessment framework for clinical stem cell applications [7, 90].

4 Clinical translation and regulatory considerations

C-14-based tracing remains a standard approach in pharmacokinetics and toxicology studies, but requires meticulous validation along with an extensive ethical review process to guarantee patient safety and regulatory compliance while achieving effective therapeutic results in cellular therapy applications [97, 98]. The precise tracking capabilities of C-14 isotopic labeling for stem cells and therapeutic assessments face numerous hurdles when applied in clinical environments [99].

The central approach for safely transition of C-14-based tracing techniques from research to human use involves microdosing [100, 101]. Microdosing enables researchers to administer small amounts of C-14-labeled cells to human participants, which limits radiation exposure but maintains the accurate measurement of stem cell activities [101]. Researchers aim to study human pharmacokinetics, biodistribution patterns, and metabolic pathways while minimizing patient risk. This approach proves essential because it enables researchers to track stem cell movement and integration in real time without subjecting patients to dangerous radiation levels [21]. Microdosing is an essential part of clinical development because it maintains C-14 doses below the radiotoxicity threshold [100, 101].

Although C-14 is a radioactive isotope, its radiological characteristics are fundamentally different from diagnostic radionuclides used in PET or single-photon emission computed tomography imaging. C-14 emits low-energy β^- particles (maximum 156 keV) with an average tissue penetration of less than 100 μm, resulting in negligible external exposure. In AMS-based microdosing studies, the total administered activity remains below 1 μCi (37 kBq). Using the International Commission on Radiological Protection (ICRP) 72 effective-dose coefficient for C-14 (5.8×10^{-10} Sv/Bq for adults), this corresponds to an effective whole body dose of approximately 21.5 μSv, which is slightly higher than 10 μSv, but still well within the IAEA-recommended safety limits ($\leq$1 mSv per year) for exempt exposures [102]. Even with 10 repeated administrations, the cumulative dose would remain less than 0.1 mSv—several orders of magnitude lower than a standard PET scan (5–10 mSv) or even a chest X-ray (0.1 mSv) [9, 103]. Such exposures are well within the limits recommended by the International Commission on Radiological Protection (ICRP Publication 103) for microtracer research studies.

At the cellular level, the estimated nucleus-absorbed dose ranged from ~ 0.01 to 0.1 mGy across labeling concentrations (1–25 nCi/mL) [7, 104]. This is below the threshold reported to induce DNA-damage signaling in the cells [94, 105]. Furthermore, C-14 labeled cells retained normal expression of cell-specific markers, functions, and proliferation after cell labeling as demonstrated in previous studies and consistent with cell viability across the applied labeling range [7].

In accordance with the *As Low As Reasonably Achievable (ALARA)* principle recommended by the ICRP and the International Atomic Energy Agency (IAEA), all experimental and clinical applications of C-14 labeling should aim to minimize radiation exposure by optimizing labeling efficiency, using the lowest possible activity, and ensuring rigorous dosimetry verification before administration [102, 103].

From an ethical perspective, these ultra-low radiation doses make C-14 tracing compatible with standard frameworks of informed consent and institutional review board (IRB) oversight. Regulatory agencies, including the FDA and EMA, require dosimetry modeling, preclinical safety data, and transparent risk communication before approving human protocols. Under such conditions, C-14 labeling represents a scientifically powerful yet ethically acceptable approach for studying stem cell fate in vivo.

While single microdosing studies using C-14-labeled cells result in extremely low radiation exposure, cumulative doses should be considered when repeated administrations or long-term tracking are planned. As C-14 decays very slowly (half-life ≈ 5730 years) and emits low-energy β^- particles with a short path length, the absorbed dose to surrounding tissues remains minimal even when labeled cells persist in vivo. Dosimetric modeling of repeated C-14 microtracer studies indicates that cumulative whole body exposure would remain below 0.1 mSv even after 10 separate administrations, which is far below the 1 mSv annual public exposure limit recommended by the International Commission on Radiological Protection [103] and supported by clinical AMS studies in humans [106]. At the cellular level, β-particle energy deposition per nucleus ($<10^{-4}$ Gy) is several orders of magnitude below thresholds associated with measurable DNA or chromosomal damage, even after prolonged intracellular retention [107]. Nevertheless, cumulative exposure assessment and long-term biosafety monitoring are recommended when planning repeated dosing in regenerative medicine trials to ensure compliance with radiological protection standards.

In addition, the potential long-term biological effects of C-14 incorporation into genomic DNA must be considered. As ^{14}C labeling replaces only a minute fraction of native carbon atoms in nucleotides, β^- decays occur at an extremely low frequency—approximately one decay event per 10^7–10^8 nucleotides per year—resulting in negligible localized energy deposition [107, 108]. Experimental investigations using C-14-labeled thymidine have

shown no increase in DNA strand breaks, chromosomal aberrations, or mutation rates at tracer-level activities [109]. Unlike short-lived positron emitters such as ^{3}H or ^{11}C, which deliver high instantaneous dose rates, the long half-life of ^{14}C (≈5730 years) produces an infinitesimal dose rate far below mutagenic threshold. Accordingly, current evidence supports that C-14 incorporation at microtracer levels is biologically inert and does not contribute to measurable mutagenic risk.

Good Manufacturing Practice (GMP)-compliant labeling protocols must be used with *microdosing to guarantee reliable and safe high-quality C-14-labeled stem cells.* Although this is a review article and no new batch-specific experiments were performed, previous studies have demonstrated that GMP-compliant radiolabeling achieves ≤ 10% label loss and ≤ 5% inter-run variability, with routine sterility and endotoxin testing ensuring safety for clinical applications [110, 111]. These procedures maintain stem cell viability and therapeutic activity while ensuring reproducibility and purity. Clinical trial protocols further require ethical oversight, informed consent, and regulatory review to confirm safe and effective human administration [112].

Clinical trial protocols require rigorous dosimetry modeling to determine the radiation dose administered to different tissues. Dosimetry simulations revealed detailed pathways for C-14-labeled stem cell distribution throughout organs and tissues, which informs the establishment of safe and effective dosage levels for humans [113]. Researchers can reduce hazards and improve therapeutic results through potential radiation exposure modeling. Researchers must perform these calculations to meet regulatory standards and ensure patient safety [114].

Clinical translation requires thorough ethical supervision through informed consent procedures and transparent communication of radiation risks to patients, along with regulatory compliance as dictated by organizations such as the FDA and EMA. Before approving clinical trial protocols, regulatory agencies examine preclinical safety data and dosimetry models and review ethical considerations to verify that these protocols meet strict safety, efficacy, and ethical standards [115].

Despite these advances, the clinical translation of C-14–based cell tracking remains highly constrained by regulatory frameworks that govern the use of radioactive materials in humans. In both the United States and the European Union, C-14-labeled cellular products are classified as combination products or advanced therapy medicinal products (ATMPs), which require dual evaluation under radiological-safety and biological-product regulations. The U.S. FDA's Center for Drug Evaluation and Research (CDER) and the European Medicines Agency (EMA) demand detailed documentation of dosimetry modeling, Good Manufacturing Practice (GMP) compliance, and radiological waste management before human authorization [116, 117].

Furthermore, ethical review boards typically restrict the use of long-lived isotopes in viable cells unless the radiation dose is demonstrably negligible and reversible, and long-term monitoring frameworks must be established to track radiological decay products or secondary biodistribution [103, 116, 118]. These requirements mean that the path from laboratory validation to first-in-human studies is lengthy and resource-intensive, emphasizing that the current technology should be regarded as preclinical and investigational rather than immediately translational. Future clinical deployment will depend on harmonized international guidelines that define acceptable exposure limits, cell-handling standards, and post-administration monitoring criteria for radiolabeled cell therapies.

Beyond regulatory and ethical considerations, the clinical implementation of C-14 tracing also faces practical constraints related to infrastructure and technology access. AMS requires large, highly specialized instrumentation, trained personnel, and strict radiological handling facilities that are typically limited to a few national research centers. The cost of AMS installation and maintenance can exceed several million dollars, and throughput capacity remains low compared with conventional imaging platforms. Consequently, the widespread adoption of C-14-based stem cell tracking in translational or multi-center studies is currently limited by access to these facilities [39, 53, 119]. Collaborative networks and centralized AMS hubs have been proposed as a potential solution, enabling shared analytical capacity while maintaining regulatory and biosafety standards.

Despite its extraordinary analytical precision, AMS remains technically and economically demanding. Each analysis requires specialized infrastructure, high-vacuum ion sources, and trained accelerator physicists, limiting accessibility to a small number of national facilities. The installation cost of biomedical AMS systems typically exceeds several million USD, and sample throughput is considerably lower than that of optical or radionuclide imaging platforms. These resource constraints currently restrict its use to research settings with centralized analytical capacity and make multi-center translational studies challenging [39, 40].

From a practical standpoint, the clinical adoption of C-14-AMS tracing also depends on a realistic cost–benefit balance compared with established cell tracking technologies. While AMS analysis entails higher operational costs (typically several thousand U.S. dollars per sample when accounting for accelerator time,

radiological handling, and quality-assurance procedures), it offers unmatched attogram-level sensitivity and the ability to quantitatively monitor labeled cells for months or even years without signal decay [26, 39]. Conventional modalities such as MRI, PET, or reporter-gene imaging provide lower per-sample costs and wider accessibility but are limited by transient signal duration, background interference, and qualitative rather than quantitative outputs [47]. Therefore, C-14 tracing should be reserved for studies where ultra-long-term quantitative tracking offers decisive biological or pharmacokinetic insights that outweigh the analytical cost.

5 Future Directions

The fields of stem cell therapy and regenerative medicine have shown promising progress, driving multiple developments to improve C-14-based tracking methods. The modernization of AMS, which is typically used for C-14 detection and quantification, should considerably enhance its sensitivity, enabling researchers to detect much smaller numbers of labeled cells. The upcoming improvements will enable precise and early-stage monitoring of stem cell therapies that involve low cell doses or hard-to-track stem cells [7, 38].

The implementation of automated sample processing will optimize the preparation and analysis stages for C-14-labeled samples [120]. Automation of sample processing reduces human mistakes while boosting throughput and improving result consistency. Automated systems will speed up and improve data collection processes for preclinical research and clinical trial applications [121, 122].

The use of hybrid methods that join C-14 labeling with additional imaging or molecular tracing techniques provides a deeper understanding of stem cell behavior [123, 124]. By combining C-14 with imaging methods such as PET and MRI, researchers can achieve comprehensive quantitative and qualitative evaluations of stem cell activities within living organisms, resulting in enhanced data reliability for cell tracking and therapy success [125].

The development of isotopic technologies such as C-14 for clinical research requires regulatory frameworks to undergo evolution. As novel isotopic methods and advanced technologies emerge, regulatory agencies must revise their guidelines and protocols to maintain safety and ethical standards [126]. Specific regulatory pathways must be established for novel isotopic labeling methods along with necessary updates to clinical trial procedures to integrate new imaging and tracking technologies [16].

6 Conclusion

C-14 labeling introduces a fundamental change in stem cell tracking methods by providing a highly precise quantitative technique for evaluating stem cell fate inside living organisms [127]. C-14 labeling offers a precise absolute measurement of individual cell activity using AMS, unlike conventional imaging or molecular assays that provide relative or indirect cellular data [7, 11, 38]. Precise tracking of transplanted cells is essential because therapeutic success and safety depend on knowledge of cell survival patterns and integration into preclinical and clinical studies [3, 128, 129].

The transformative nature of this technology lies in its ability to address two central challenges in regenerative medicine [130]. The dual objectives in regenerative medicine research include measuring how transplanted cells aid tissue repair and functional recovery together with identifying harmful outcomes such as ectopic engraftment or tumorigenesis [92]. C-14 labeling creates a new benchmark for tracking cell-based treatments by allowing long-term high-resolution stem cell monitoring without the need for reporter genes or invasive biopsy methods [11].

C-14-based tracing creates a connection between preclinical proof-of-concept research and clinical application. Early phase trials utilized microdosing protocols to obtain essential biodistribution and dosimetry data while maintaining the patient risk very low [131]. This approach achieves dual goals by improving therapeutic mechanism insights while providing regulatory approval bodies with stronger evidence. C-14 labeling enables the development of stem cell therapies that follow a rational and evidence-supported pathway, which accelerates their adoption in clinical practice [101].

Despite its remarkable precision, C-14–based AMS tracing still faces several methodological and translational limitations. First, the requirement for specialized AMS facilities, high operational costs, and limited accessibility restricts widespread adoption and multi-center standardization [39, 53]. Second, variability in graphite preparation, isotope ratio normalization, and inter-laboratory calibration continues to pose challenges for data reproducibility [30, 31]. Third, existing research remains largely confined to proof-of-concept models, and rigorous comparative or clinical validation studies are scarce. Addressing these issues will be crucial for establishing C-14 tracing as a robust and regulatory compliant platform for clinical translation.

The ongoing combination of C-14 tracing technology with molecular imaging, transcriptomic profiling, and spatial omics methods will enhance our understanding of stem cell behavior in complex biological systems. Ongoing advances in the AMS technology will deliver

better sensitivity and wider accessibility, expanding its use across various clinical environments [132].

C-14 labeling functions beyond tracking capabilities to become a transformative analytical platform that strengthens scientific rigor and enhances the translational value of regenerative medicine [133]. The adoption of this technology will provide deeper mechanistic insights while optimizing therapy design and improving the safety and efficacy of cell-based treatments for various diseases and injuries [7, 38].

Continued methodological refinement, cost reduction, and inter-laboratory standardization will determine whether this technology can move beyond experimental validation and realize its full clinical potential. To conclude, although C-14–based AMS tracing provides an exceptionally precise and long-term quantitative platform for monitoring stem cell fate, several limitations must be acknowledged. The need for highly specialized AMS facilities and technical expertise restricts broad accessibility and prevents large multi-center validation studies. Methodological variation across laboratories, including differences in sample preparation and isotope ratio calibration, can affect reproducibility. Additionally, most published work remains at the proof-of-concept stage, with limited direct comparison to existing imaging-based tracking modalities. These limitations highlight the need for continued standardization, cost reduction, and coordinated multi-center benchmarking efforts to fully establish the translational readiness of this technology.

7 Competing interests

The authors declare no competing interests.

Abbreviations

C-14	Carbon-14
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PCR	Polymerase chain reaction
AMS	Accelerator mass spectrometry
iPSCs	Induced pluripotent stem cells
GMP	Good Manufacturing Practice
ICRP	International Commission on Radiological Protection

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Author contribution

S.K contributed to conceptualization, writing—original draft, writing—review and editing. M.R contributed to literature search, prepared Figs. 1–3, editing. S.K and M.R contributed equally to this work as co-first authors. Y.P and H.Y contributed to literature search, visualization, and editing. S.M contributed to funding acquisition, resources, writing–review, and supervision. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

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