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Perspective

Aligning Intrinsic Capacity and Geroscience: Linking Function with Biology

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ABSTRACT: As population ages globally, the agenda of healthy aging has emerged as a critical priority. For addressing the evolving needs of the aging population, the World Health Organization (WHO) introduced the concept of Intrinsic Capacity (IC), which is defined as the composite of all physical and mental capacities. IC brings a major paradigm change, shifting the focus from disease to function and optimization of IC through life has been suggested to be required for achieving healthy aging. In parallel, geroscience is an emerging discipline aiming to understand the biology of aging and developing strategies to slow the aging process and thus prevent age-related functional decline and chronic diseases. This narrative review explores the conceptual and translational connection between IC and geroscience, proposing that IC may serve not only as a measurable indicator of global function but also as a potential target for geroscience interventions. We discuss how the hallmarks of aging underlie declines in the domains of IC and summarize emerging gerotherapeutic approaches that may potentially optimize IC. We further discuss the possibility of integrating IC into geroscience-informed clinical and public health frameworks, emphasizing its value in guiding preventive and personalized strategies for healthy aging.

Keywords: aging, biology of aging, hallmarks of aging, gerotherapeutics, geriatrics, longevity

1. Introduction

The global rise in population aging has placed the agenda of "healthy aging" not only at the forefront of public health priorities but also from a biomedical perspective. The World Health Organization (WHO) defines healthy aging as the process of optimizing functional ability, which enables well-being even during older age [1, 2]. The WHO proposed intrinsic capacity (IC) to be the core element of functional ability and healthy aging [1]. IC comprises all mental and physical capacities that a person can draw on and includes multiple domains. There has been a great interest in IC research from a clinical perspective [3]. At the same time, there is also a greater focus on biomedical strategies to optimize IC, particularly from a geroscience approach [4].

Geroscience is comparatively a new field of research which focuses on understanding the mechanisms of the aging process and targeting them to ameliorate age-related negative outcomes [5–7]. Several chronic conditions and geriatric syndromes are associated with old age, and geroscience advocates on shifting the focus from treating disease towards slowing the aging process [6].

The concept of IC appears as an attractive entity for considering age-related functional decline as it captures the global functional status of an individual, hence, included in the 11th International Classification of Diseases (ICD) [8]. No matter the decline in IC as a result of accelerated aging or chronic disease, it could serve as an important outcome for geroscience trials or could even itself serve as the target (i.e., targeting the affected domains). In this review, we establish the potential link

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between IC and the geroscience discipline and explore geroscience strategies to maintain and enhance IC.

2. The concept of Intrinsic Capacity:

The WHO World Report on Ageing and Health introduced the concept of IC in 2015 [1]. The WHO postulates IC as the core framework for monitoring and assessing older individuals and optimizing IC throughout life is proposed as the way towards achieving healthy ageing. IC consists of multiple domains, including locomotion, cognition, psychology, sensory (hearing/vision), and vitality [2]. The recommended methods for assessing these domains are shown in Table 1.These domains of IC are suggested to be interlinked and influence each other through various mechanisms [9]. Clinicians and aging researchers are being attracted by this novel concept, as not only does IC provide targets to intervene clinically [2, 10], but these various domains could serve as the outcome measures of geroscience strategies targeting age-related conditions [4, 7]. Nevertheless, the majority of the real-world studies on IC focus on improving the functional ability of older adults through integrated care models such as ICOPE [11–13] which is a model proposed by the WHO. At the same time, attempts are also being made to develop IC-based functional ability index [14] or the growth chart [15]that could help monitor the health status of aging individuals. Distinctions should be made with some related constructs such as frailty [16], resilience, and reserve [17, 18]to maintain conceptual clarity, as they share some similarity with IC [18, 19] and are considered important in geroscience [4] (see Box 1). In the continuum of aging and functional ability, IC is present throughout life course, while frailty is more distinct in later life. Loss of resilience and decline in reserve contributes to decline of IC and manifestation of frailty, however, resilience and reserve are challenging to assess in practice. From a geroscience perspective, targeting IC could be more relevant than targeting frailty, as interventions optimizing IC may mitigate disability and late life frailty. At the translational level, effort is being made to develop an IC-based epigenetic clock [20] , identifying unique biomarkers of IC decline [21–24] and attempts are being made to develop preclinical models of IC [25] .

Box 1. Definitions of common constructs related to Intrinsic Capacity.

Frailty: A state of reduced physiological reserve and increased vulnerability to stressors, resulting in higher risk of adverse events like disability, hospitalization, and mortality.

Resilience: Dynamic ability of an individual to withstand, adapt or recover from stressors. Physical resilience (commonly used in aging research) specifically denotes the ability to resist decline or recover from functional decline after a major health stressor and its operationalization requires the consideration of "system, state, and stressor".

Reserve: It refers to the underlying accumulated capacity within physiological systems that enable individuals to tolerate/adapt age-related changes. Multiple forms of reserves (e.g., cognitive, psychological etc.) are proposed to exist, and their depletion could contribute to the manifestation of functional impairment.

2.1 Preclinical operationalization of Intrinsic Capacity

Although IC is a human-centered construct, preclinical models (e.g., rodent models) are highly relevant for translational aging research, hence should be briefly discussed. To our knowledge, studies on direct assessment of IC in animal models are very limited and the INSPIRE cohort represents the only ongoing initiative explicitly aiming to operationalize IC in preclinical settings [25]. The domains of IC can be approximated in preclinical models using multidimensional functional phenotyping and used as a composite IC score. We have included the potential preclinical measures([25–27]) in Table 1.

3. The geroscience hypothesis

Geroscience is an emerging discipline which primarily aims to slow down the aging process, thereby delaying or preventing many chronic diseases (including existing multimorbidity) that are considered as the cause of functional decline and disability in late life [5, 28, 29]. In other words, geroscience aims to develop strategies to extend healthspan, which means increased lifespan but in good health [6]. Today, human life has extended substantially; however, there is a huge gap between overall lifespan and healthspan [30]. Countries face a huge challenge to fight this gap, while high-income countries invest large amount of resources in developing long-term care and geriatric programs, the low- and middle-income countries (LMICs) largely lack resources to address the gap. Geroscientists believe that with suitable intervention techniques, slowing the aging process, we could save the resources required to address the health-related burden of population aging globally [29].

Table 1. Measures for the assessment of Intrinsic Capacity in human and preclinical rodent models.

Intrinsic Capacity domains	Measures for the assessment of Intrinsic Capacity in human	Potential measures for the assessment of Intrinsic Capacity in rodents
Cognition	Cognitive decline: Screening: Three words recall test, Orientation test Confirmatory: Mini-Cog, MoCA, MMSE, GPCOG	Y-maze to assess spatial working memory
Locomotion	Limited mobility: Screening: Chair rise test Confirmatory: SPPB	Open-field test and running speed using the incremental treadmill test
Vitality	Malnutrition: Screening: Weight loss, Appetite loss Confirmatory: MNA/ MUST/ SCREEN/ SNAQ65+	Percentage body weight changes (over 1 month), grip strength, tight-rope test, echocardiography, urinary function
Psychology	Depression: Screening: "Over the past two weeks, have you been bothered by feeling down, depressed or hopeless/ little interest or pleasure in doing things?" Confirmatory: PHQ-9, GDS	Open-field test to assess anxiety-like behaviors
Sensory	Hearing loss: Screening: Whisper test Confirmatory: Audiometry	Auditory brainstem responses
	Vision impairment: Screening: difficulties in seeing, having eye diseases or currently under medical treatment for diabetes and hypertension? Confirmatory: Distance and near vision test	Optokinetic reflex/Optomotor reflex assays

Abbreviations: MoCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination; GPCOG: General Practitioner Assessment of Cognition; SPPB: Short Physical Performance Battery; MNA: Mini Nutritional Assessment; MUST: Malnutrition Universal Screening Tool; SCREEN: Seniors in the Community Risk Evaluation for Eating and Nutrition questionnaire;SNAQ65+:Short Nutritional Assessment Questionnaire 65+; PHQ-9: Patient Health Questionnaire; GDS:Geriatric Depression Scale

4. Hallmarks of aging as the mechanism linking Intrinsic Capacity and geroscience

IC represents the biological substrate of age-related functional ability, reflecting the interplay between physiological systems and the external environment. The physiological systems are influenced by the fundamental hallmarks of aging, which are considered potential intervention targets from a geroscience perspective [6]. The nine hallmarks of aging were first proposed in 2013 [31]and were recently updated, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis [32]. Several hallmarks of aging provide mechanistic pathways linking molecular and cellular dysfunctions to declines in specific domains of IC. For e.g., mitochondrial dysfunction characterized by increased reactive oxygen species production, impaired apoptotic signaling and disrupted calcium homeostasis leads to reduced ATP production, causing age-related muscular decline-impacting locomotor function [33] and reduced vitality [34]. A detailed discussion on the mechanism involved is beyond the scope of this review. Below, we discuss various biological processes linking the hallmarks of aging with decline in IC (Fig. 1)

4.1 Locomotion: Humans are known to have impairment in locomotory capacity as we age, which could be because of decline in muscular function and muscle loss, such as in sarcopenia [35] or as a result of overall decline in physiological systems like in frailty- a state of reduced homeostasis and vulnerability to negative outcomes [16]. Several hallmarks of aging, including mitochondrial dysfunction [33], cellular senescence [36, 37], stem cell exhaustion [38, 39], altered intercellular communication [40, 41] and chronic inflammation [35] could largely influence the locomotory capacity.

4.2 Cognition: A substantial portion of older individuals experience some forms of cognitive decline. Cognitive decline could sometimes be present in a dominant form, for instance, in diseases like Alzheimer's and Parkinson's [42], while some individuals may just experience mild cognitive impairment or others with intact cognitive capacity even in late life. Chronic inflammation or inflammaging, mitochondrial dysfunction, oxidative damage, impaired autophagy function, impaired adaptive stress response signaling, stem cell exhaustion, genomic instability, epigenetic alterations, dysregulated energy metabolism and dysregulated neuronal calcium homeostasis have been

proposed to be the hallmarks of "brain aging" [43], which also largely overlap with the hallmarks of aging.

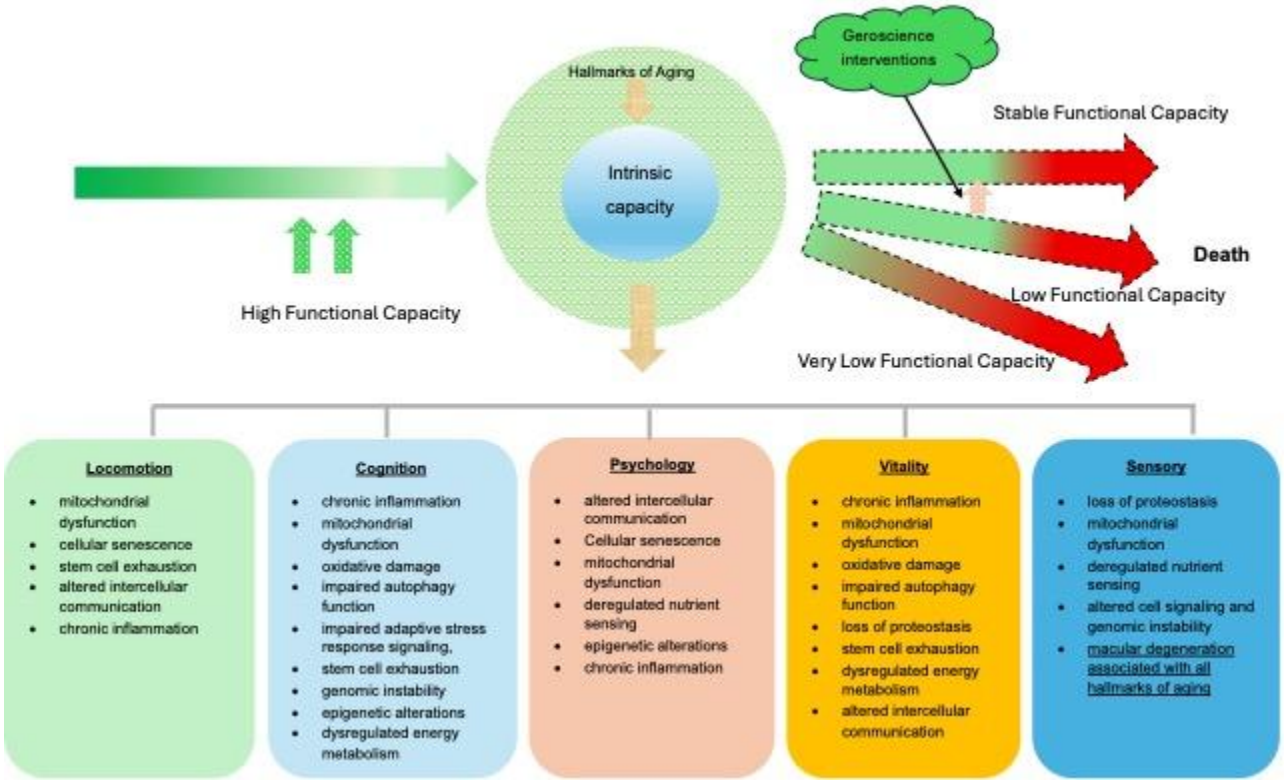

Figure 1. Mechanism linking the hallmarks of aging with decline in Intrinsic Capacity. A high and stable functional capacity is present during early life. With the increase in age several hallmarks of aging are activated which could potentially impact the intrinsic capacity of aging individuals. Decline in intrinsic capacity could lead to reduced functional capacity (multiple trajectories) and disability whereas optimization of intrinsic capacity using a Geroscience approach could lead to a stable functional capacity preventing/delaying disability in later life.

4.3 Psychology: In the WHO conceptualization of IC, depression is considered as the psychological condition of interest, which is highly prevalent in older individuals [44]. Depression in older adults is a major cause of disability and functional limitation [45] and has been shown to be associated with accelerated biological aging [46]. Cellular senescence, altered intercellular communication, mitochondrial dysfunction, deregulated nutrient sensing, epigenetic alterations and inflammaging have been suggested to be the hallmarks of aging, largely linked with depression [47].

4.4 Sensory: Hearing and vision loss are included in the sensory domain of IC [2]. Older adults are known to have a high prevalence of sensory impairments, which are also linked with cognitive decline [48] and disability in late life [49]. Hallmarks of aging, like mitochondrial dysfunction, genomic instability, inflammaging, disabled macroautophagy and other epigenetic alterations have been suggested to be associated with hearing loss [50]. Vision loss associated with aging could be abnormalities of the lens (e.g., cataracts) and linked with several hallmarks of aging, such as loss of proteostasis, mitochondrial dysfunction, deregulated nutrient sensing, altered cell signaling and genomic instability [51]. Vision loss from age-related macular degeneration has been proposed to be linked with almost every hallmarks of aging and suggested to share mechanistic features of chronic diseases like Alzheimer's, Parkinson's or cardiovascular diseases [52].

4.5 Vitality: Poor nutritional status has been considered as the primary measure of the vitality domain. Anorexia of aging defined as reduced appetite and low intake of food in older age affects one quarter of older adults [53]. Malnourished older adults are generally frail and are prone to negative outcomes [53]. Several hallmarks of aging could be linked with poor vitality, mainly chronic inflammation (driver of physical decline) [54, 55], mitochondrial dysfunction (being related with energy and fatigue as the marker) [34], deregulated nutrient-sensing (potential involvement of impaired insulin signaling) [56], loss in proteostasis (proteotoxic stress mechanism triggering frailty) [57] and altered

intercellular communication (endocrine dysregulation) [58].

5.Geroscience strategies to optimize Intrinsic Capacity

As discussed before, IC could serve as an explicit outcome measure for geroscience trials for evaluating functional changes. At the same time, older adults with IC decline could benefit from several gerotherapeutics that are being actively investigated for targeting different hallmarks of aging [6, 7, 29]. In the Targeting Aging with MEtformin (TAME) study metformin is used to slow the aging process, targeted at preventing age-associated chronic diseases and functional decline [59]. Metformin has been suggested to influence a number of hallmarks of aging, like modulating mitochondrial function, lowering telomere attrition, and cellular senescence, etc. [60]. Similarly, caloric restriction is considered another geroscience approach that might have implications for optimizing IC in older adults. The CALERIE trial showed caloric restriction to be effective in reducing inflammatory markers, improving insulin sensitivity index and reducing metabolic syndrome score compared to controls [61]. The clinical findings were also supported by further analysis of muscle biopsies of the CALERIE participants, showing several hallmarks of aging, including DNA repair, mitochondrial biogenesis, apoptosis, and inflammation to be improved [62]. At the same time, human studies have also shown caloric restriction to have improvement in cognition [63], and muscle quality [62]. Physical exercises are well known to improve functions in older adults and using a multicomponent approach IC impairment was shown to improve [64]. Role of physical exercise as geroprotectors is being increasingly accepted [65], including studies showing beneficial outcomes in brain aging [66] and cardiovascular aging [67].Similarly, Rapamycin and its derivatives are also being extensively investigated for their ability to inhibit mTOR- a key driver of aging and age-related conditions [68]. A recent systematic review of human studies suggested Rapamycin and its derivatives to be effective in improving the age-related physiological parameters [69]. Furthermore, senolytics targeting cellular senescence have been considered gerotherapeutics with high hopes [70, 71]. A recent study showed two senolytic agents, Dasatinib and Quercetin to improve cognition and mobility in individuals at risk of Alzheimer's disease [72]. A recent review by the team proposing the "hallmarks of aging" suggested the discipline of geroscience to have a greater focus on gerogenes that are responsible for accelerated aging processes using gerosuppressors [6], which could have implications for maintaining several domains of IC that are influenced by gerogenes. Additionally, the use of regenerative medicine and cellular therapies should also be acknowledged as potential therapies to optimize IC. Past studies have shown mesenchymal stem cells (MSCs) to be useful in improving physical function in frail older adults and reducing inflammation [73] , shown to have beneficial effect in reducing cognitive decline and neuroinflammation in mild Alzheimer's disease [74]. Other nutraceuticals such as nicotinamide adenine dinucleotide (NAD+) boosters [75], Beta-hydroxy-beta-methylbutyrate (HMB) [76] are known to improve muscle function and protect against neurodegeneration [77]. We have summarized some of the gerotherapeutics potentially useful for optimizing IC in Table 2.

Table 2. Geroscience interventions having potential beneficial effects for optimizing Intrinsic Capacity.

Geroscience interventions	Primary hallmarks of aging targeted	Intrinsic Capacity domains to be potentially affected
Metformin	mitochondrial function, lowering telomere attrition, cellular senescence, deregulated nutrient sensing	potentially influence all domains
Caloric restriction	epigenetic alterations, mitochondrial dysfunction, deregulated nutrient sensing, apoptosis, and inflammation	cognition, locomotion, vitality
Rapamycin and its derivatives	deregulated nutrient sensing, loss of proteostasis, mitochondrial dysfunction, cellular senescence	cognition, locomotion, vitality
Senolytics (Dasatinib and Quercetin)	cellular senescence, altered intercellular communication, chronic inflammation	cognition, locomotion, psychological capacity
Mesenchymal stem cells	chronic inflammation, stem cells exhaustion, altered intercellular communication	cognition, locomotion, vitality, sensory
Nutraceuticals (NAD+ boosters, Beta-hydroxy-beta-methylbutyrate (HMB)	chronic inflammation, mitochondrial dysfunction, epigenetic alterations, deregulated nutrient sensing	cognition, locomotion, vitality
Various forms of physical and cognitive exercise	potentially influence all hallmarks of aging	potentially influence all domains

Note: Several other interventions could have the potential for optimization of intrinsic capacity, we here included strategies that have comparatively higher-level evidence in human.

Additionally, beyond single targeted interventions, a key principle of geroscience is the holistic targeting of common biological mechanisms across multiple organ systems. Several gerotherapeutics discussed above, like Metformin, Rapamycin or cellular therapies are known to act at multisystem level and could have higher beneficial effects on improving multiple functions in older adults, which should be carefully investigated in future studies. Moreover, emerging evidence suggest combination therapies could result in additive or synergistic benefits compared to single domain interventions [78]. Multicomponent interventions are well-established to have a greater beneficial effects in improving physical and cognitive functions in older adults [78, 79]. While geroscience studies implementing combination-gerotherapeutics are scarce, previous findings support the rationale for integrated approaches to optimize IC in human, hence should be explored.

6. Integrating geroscience, geriatrics, and public health: the potential role of Intrinsic Capacity

The original purpose of introducing the concept of IC by the WHO was to highlight the need to shift from a disease-centered approach to a function-centered paradigm for properly addressing the care needs of growing number of older adults [2]. A large portion of older adults have complex clinical presentations along with geriatric syndromes that are difficult to address using the traditional models of care, as suggested in the landmark paper by Tinetti [80]. Geroscience advocates for a more preventive approach, i.e., slowing down the aging process and maintaining physiological resilience to prevent chronic diseases and geriatric syndromes. The integration of geroscience and geriatric medicine requires bridging the gap between aging research and clinical practice. This integration calls for an openness towards new geroscience approaches, such as the use of aging biomarkers for screening high-risk individuals and use of established gerotherapeutic interventions in clinical practice. Integrating these entities will shift the care model from a reactive (i.e., based on disease management) towards a much proactive approach of maintaining function and optimizing IC. Nevertheless, this approach could be expanded to other specialties managing chronic conditions on a regular basis and could be integrated into the health system. Public health programs should prioritize healthspan to lifespan, which will potentially enhance personalization of care and align aging research, clinical practice, and public health policy toward the shared goal of achieving healthy aging. The WHO-ICOPE care model [81] provides such an opportunity to include geroscience into the integrated care model, which indeed has to be tested. In fact, the INSPIRE study in Toulouse aims at integrating geroscience and geriatrics embedded in their local health system [82]. The team aims to create a geriatric growth chart based on IC domains [15], which could be useful to monitor the functions of older individuals in daily life or potentially be used in clinical trials. Furthermore, an IC-specific epigenetic clock has been recently developed that was associated with changes in some hallmarks of aging and functional endpoints [20]. Thus, IC emerges as a unifying construct, bridging the scientific principles of geroscience, clinical perspective of geriatrics and population-level focus of public health together.

7. Future perspectives

The alignment of IC and geroscience heralds a new era of aging research and geriatric care suitable for the world rapidly being dominated by older populations. For advancing precision geroscience, future studies should use IC as a functional endpoint along with other biological markers. Additionally, larger studies targeting IC impairments using the existing geroscience approach could enable us to better understand the link between the hallmarks of aging and IC. More IC-based biomarkers that are easy to assess and are sensitive to longitudinal changes are needed for monitoring functional decline in older adults. Translational integrated care models like ICOPE are needed to implement combined (i.e., gerotherapeutics, geriatrics and public health) intervention strategies at the population level, which might be quite early to achieve. Raising awareness on geroscience is very essential, especially among clinicians, for advancing personalized care plans for aging individuals. A global effort involving geroscientists, geriatricians, public health specialists, and policymakers will be essential to translating biological discoveries into interventions that preserve IC across diverse population settings. It is also necessary to ensure access to such approaches globally, including for those residing in LMICs.

Despite the strong conceptual framework of aligning geroscience with IC, several challenges must be acknowledged. For instance, aging process being heterogeneous, several strategies discussed here may not exhibit uniform effectiveness in all older adults. Optimal dosing, duration of intervention, and long-term safety of several gerotherapeutics are also some challenges that need to be addressed. Finally, it should also be acknowledged that although geroscience approaches are very promising, there are several regulatory hurdles that need to be addressed [83].

8. Conclusion

The construct of IC provides a holistic framework for quantifying and monitoring the global functional outcomes of aging, while geroscience provides the biological foundation to understand and intervene in the aging process. Alignment of these two paradigms establishes a continuum from the biology of aging to clinical and population-level action. IC could serve as a bridge integrating geroscience discoveries into healthy aging strategies. Connecting IC and geroscience holds the potential to not only extend the lifespan but also the healthspan, adding quality and wellbeing to later life.

Declaration of interest

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution

Sha Zhu, Lihua Tao, Cheng Cheng Fan and Yongzhe Wei contributed to the initial drafting of the manuscript, including literature search. Jagadish K. Chhetri and Piu Chan critically revised the manuscript. Jagadish K. Chhetri responsible for the conceptualization of the manuscript. All authors approved the final version of the manuscript.

Ethics and Consent to Participate declarations

Not applicable.

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