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New reference limits for cardiac troponin T and N-terminal b-type natriuretic propeptide in elders

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ABSTRACT

Background and aims: Our aim was to define reference limits for cardiac troponin T (cTnT) and N-terminal pro B-type natriuretic peptide (proBNP) that would better reflect their concentrations in older people. In addition, the incidence of acute myocardial infarctions (AMIs) was studied using these reference limits in an older population with and without previous heart diseases.
Materials and methods: A population-based study with a ten-year follow-up. The reference population was formed by 763 individuals aged over 64 years, with no diagnoses of heart or kidney diseases.
Results: There was a significant increase in cTnT and proBNP concentrations with age. The 99 % reference limits for cTnT were 25 ng/L, 28 ng/l, 38 ng/l, and 71 ng/l for men in five-year-intervals starting from 64 to 69 years to 80 years and older, and 18 ng/L, 22 ng/l, 26 ng/l, and 52 ng/L for women, respectively. The 97.5 % reference limits for proBNP were 272 ng/L, 287 ng/l, 373 ng/l and 686 ng/L for men, and 341 ng/L, 377 ng/l, 471 ng/l, and 794 ng/L for women, respectively. Elevated proBNP was statistically significantly associated with future AMIs in subjects with and without a previous heart disease.
Conclusions: Age-specific reference limits for cTnT and proBNP are needed to better evaluate cardiac symptoms.

1. Introduction

Although the diagnosis of acute myocardial infarction (AMI) has been updated several times, the measurement of cardiac troponins (cTns) is still required. The diagnosis of AMI requires detection of an elevated cTn value above the 99th percentile upper reference limit (URL) with a rise or fall of cTn values [1].

High-sensitivity cTn assays are increasingly used [1]. The high performance of sensitive assays have improved the early diagnosis of myocardial infarctions [2–4]. As the high-sensitivity assay of cardiac troponin T (cTnT) has a low analytical detection limit, it is able to measure concentrations of cTnT in a significant proportion of healthy adults as well, and in most older individuals [3,5–8]. Although cTns are mainly used for the diagnosis of acute coronary syndrome, various other conditions which include cardiomyocyte death also contribute to elevated troponin levels such as non-ischemic acute and chronic heart diseases but also chronic kidney disease [3,5–10]. Studies have shown an association between elevated cTnT and all-cause and cardiovascular mortality in populations with or without cardiac disease [6,8,9,11].

The level of cTnT increases with age as shown in a number of studies

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[3,6,7,9,10,12–15]. Still, the reference ranges established for adult population are recommended although the cut-offs are not based on older population that is highly prevalent in emergency care and other health care appointments.

The concentrations of natriuretic peptides including N-terminal pro B-type natriuretic peptide (proBNP) rise in left ventricular dysfunction and have a significant role in the diagnosis and monitoring of heart failure (HF) [16,17]. A background of cardiovascular disease and especially previous myocardial heart infarction makes HF more likely. Renal impairment and atrial fibrillation may also increase the levels of natriuretic peptides [17,18].

The concentration of proBNP increases with age [19–24]. The selected threshold value has a significant impact on the proportion of results that are considered elevated which is why age-specific reference limits are needed. However, specific cut-offs to rule-in or rule-out acute HF in different-age groups have been developed and are widely applied [25].

The aim of this study was to define reference limits for cTnT and proBNP in an older Finnish population that would better reflect their concentrations in older population and could be applied in clinical use. In addition, we assessed the association of cTnT and proBNP with the 10-year incidence of fatal and non-fatal AMIs in the study population.

2. Material and methods

2.1. Study design and population

This study is part of a longitudinal epidemiological study carried out in the municipality of Lieto in Southwestern Finland [26]. All persons born in or prior to the year 1933 (n = 1596) were invited to participate in the baseline examination which was carried out between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or did not respond, leaving 1260 (82 %) participants, 533 men and 727 women.

All individuals with a kidney disease (International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] codes N00–N29) at baseline (n = 62) were excluded. Of those without kidney diseases, 435 already had a diagnosis of a heart condition (ICD-10 codes I20–I25, I30–I52 including ischemic heart diseases and other heart diseases) at baseline and were also excluded from the reference population. This left us with 763 individuals who formed the reference population for cTnT and proBNP.

The 435 participants with a previous diagnosis of a heart disease at baseline were used to test the association of our newly created reference ranges with the incidence of AMIs in older population with a previous heart condition.

Cross-sectional data collected between March 1998 and September 1999 were used as baseline information. All study participants were clinically carefully examined, and blood samples were taken, and aliquots of serum stored. The clinical examination included a comprehensive interview with history, lifestyle, and previous diagnoses, Rose questionnaire, numerous laboratory analyses and an electrocardiogram examination [26].

The data on the participants' diagnoses for AMIs and data on mortality were collected from the municipalitýs electronic patient record system, the Finnish Hospital Discharge Register provided by the National Institute of Health and Welfare, and the Finnish Cause of Death Registry, from the Official Statistics of Finland, from baseline examination up till the end of 2008, providing a follow-up-period of 10 years. The diagnosis for AMI was based on ICD-10 codes I21 and I22.

2.2. Laboratory measurements

Venous blood samples were obtained with minimal stasis between 8 and 10 a.m. after overnight fast at Lieto health centre. All participants were given verbal and written instructions before laboratory visit.

Blood samples were collected, centrifuged and aliquots of serum were stored at −70 °C. The analyses of hs-cTnT and pro-BNP were performed from previously unthawed stored samples. Samples were analysed at the Laboratory of Turku University Hospital.

The determination of hs-cTnT and proBNP were performed on a Cobas® 8000 e801 analyzer using electrochemiluminescence immunoassay (ECLIA) method (Roche Diagnostics, Mannheim, Germany; for hs-cTnT the limit of detection (LoD) 3 ng/L, the limit of quantification (LoQ) (10 % coefficient of variation (CV value)) 13 ng/L, and for proBNP LoD 5 ng/L, LoQ (20 % CV value) 50 ng/L). The mean coefficients of variation for two-level controls were 3.0 % and 3.8 % for cTnT, and 2.7 % and 2.8 % for proBNP.

2.3. Statistics

Mann-Whitney *U* test was used to compare the cTnT and proBNP concentrations between age groups and genders.

cTnT and proBNP values were log transformed for reference limit calculations due to skewed distribution. Normal distribution method was used to calculate 97.5 % reference limits (mean1.96 × standard deviation [SD]) with their corresponding 95 % confidence intervals after exclusion of outliers according to the 3 SD criterion. For cTnT we defined also the 99 % reference limit (mean + 2.33 × SD) that is recommended for the diagnosis of AMI[1]. After the reference limits were calculated, the values were back-transformed to the original units.

Hazard ratios (HRs) and their 95 % confidence intervals (CI) for the incidence of infarctions were calculated using Cox proportional hazard models. The follow-up period was calculated from the baseline measurements to the end of the follow-up period of 10 years or to the death of the individual. Death was used as a competitive factor in the cox regression analysis. P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.4. Ethics

The Lieto Elderly Study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol (Diary number 112/1802/2015). Participants provided written informed consent for the study.

3. Results

3.1. Baseline characteristics

The reference population was formed by 763 individuals, 308 men and 455 women aged over 64 years. The mean age of the men was 72.1 years (SD 6.2), and the mean age of the women 72.8 years (SD 6.4). There were 435 participants with a previous heart disease, 193 men, whose mean age was 73.5 years (SD 6.4) and 242 women, whose mean age was 76.3 years (SD 7.5).

The median concentrations of cTnT among the reference population were 10.9 ng/L (interquartile range [IQR] 8.2–15.2) for men, and 9.2 ng/L (IQR 6.5–12.2) for women. The median concentrations of cTnT among the population with a previous heart disease were 14.1 ng/L (IQR 10.1–22.1), and 10.7 ng/L (IQR 7.8–19.0), respectively.

The median concentrations of proBNP among the reference population were 81 ng/L (IQR 47–153) for men and 123 ng/L (IQR 75–210) for women. The median concentrations of proBNP among the population with a previous heart disease were 201 ng/L (IQR 94–617), and 259 ng/L (IQR 116–635), respectively.

The median concentrations of cTnT and proBNP in different age groups among the reference population are shown in Table 1. The relation of cTnT proBNP concentrations with age in the reference population can be seen in Fig. 1.

Table 1
Median concentrations and interquartile ranges (IQR) of cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP) in different age groups among the reference population.

	n	Median concentration of cTnT (ng/L)	IQR	Median concentration of proBNP (ng/L)	IQR
Men					
64–69 years	138	9.0	6.9–12.1	64	34–118
70–74 years	85	10.7	8.3–13.4	75	47–121
75 to –79 years	49	14.6	10.7–19.4	115	79–186
Over 80 years	38	16.7	13.3–31.2	131	66–239
Women					
64–69 years	176	6.9	5.3–9.5	91	59–158
70–74 years	130	8.8	6.8–11.2	113	76–170
75–79 years	77	10.4	7.7–13.9	133	103–214
Over 80 years	76	15.3	10.9–21.7	219	125–355

3.2. Reference limits

The reference limits were defined separately for both genders in four age groups because of statistically significant age group and gender differences in cTnT and proBNP values.

For cTnT, we calculated a 99 % reference limit of 25 ng/L for men aged 64 to 69 years, 28 ng/l for men aged 70 to 74 years, 38 for men aged 75 to 79 years, and 71 for men aged 80 years and older, and 18 ng/L, 22 ng/l, 26 ng/l, and 52 ng/L for women, respectively. The 97.5 % reference limits for proBNP were 272 ng/L, 287 ng/l, 373 ng/l and 686 ng/L for men, and 341 ng/L, 377 ng/l, 471 ng/l, and 794 ng/L for women, respectively (Table 2).

3.3. The associations with the ten-year incidence of acute myocardial infarctions

There were 109 new AMIs in the whole study population during the 10-year follow-up period, and 53 of those in the population who already had a previous diagnosis of a heart disease.

Out of the 401 participants with a heart disease and normal cTnT level at baseline 46 (11 %), and out of the 34 participants with an elevated cTnT seven (21 %) had an AMI during the follow-up period (Table 3).

Two hundred and ninety-nine participants with a heart disease had a normal proBNP level at baseline and 29 (10 %) of those had an AMI whereas 136 participants with a heart disease had an elevated proBNP level and 24 (18 %) of those had an AMI during the follow-up period (Table 4).

According to the Cox regression analyses, elevated cTnT above the 99 % reference limit tended to be associated with the incidence of AMIs during the 10-year follow-up period among participants with or without a previous heart disease but the associations were not statistically significant. Elevated proBNP was statistically significantly associated with the incidence of AMIs both among participants with and without a previous heart disease.

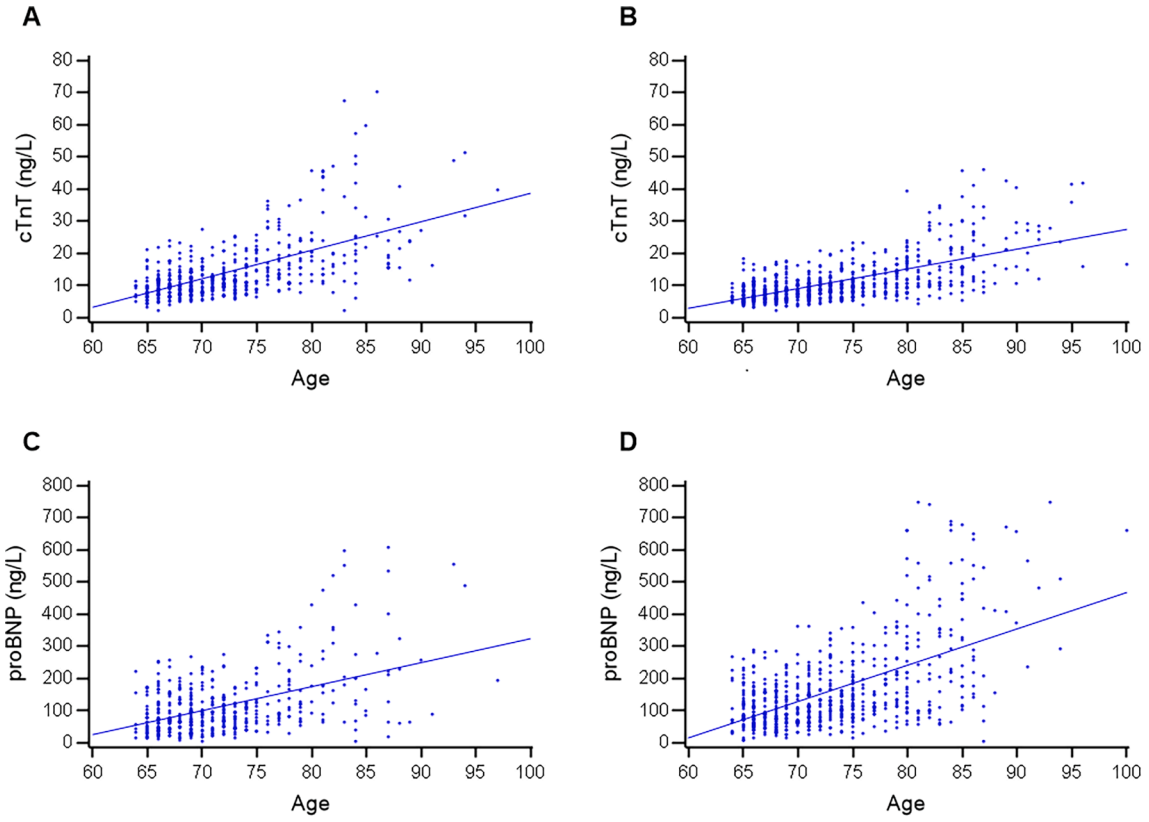

Fig. 1. The relation of cardiac troponin T (cTnT) in men (A) and women (B), and N-terminal natriuretic b-type propeptide (proBNP) in men (C) and women (D) with age in the reference population.

Table 2
Reference limits and their 95% confidence intervals (CI) for cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP).

	cTnT					proBNP		
	n	97.5 % reference limit	95 % CI for reference limit	99 % reference limit	95 % CI for reference limit	*n*	97.5 % reference limit	95 % CI for reference limit
Men								
64–69 years	136	22	19–24	25	22–29	133	272	217–342
70–74 years	82	24	21–28	28	24–32	78	287	217–380
75–79 years	48	32	27–39	38	31–46	44	373	273–509
80 years and older	37	58	42–79	71	52–97	31	686	417–1130
Women								
64–69 years	174	16	14–18	18	17–20	168	341	285–409
70–74 years	124	19	17–21	22	19–24	122	377	312–455
75–79 years	75	23	19–27	26	23–31	73	471	366–607
80 years and older	74	43	35–53	52	42–63	67	794	603–1045

Table 3
Number of participants with normal or elevated levels of cardiac troponin T (cTnT) above the 99% reference limit who had an acute myocardial infarction (AMI), did not have AMI, or deceased of other reasons during the 10-year follow-up period, and hazard ratios (HR) and their 95% confidence intervals (CI) of elevated cardiac cTnT for AMI for participants with or without a previous heart disease at baseline.

	n	AMI during the follow-up *n* (%)	No AMI and alive at the end of the follow-up *n* (%)	Deceased of other reasons *n* (%)	HR (95 % CI)	p-value
Participants with a previous heart disease						
Normal cTnT at baseline	401	46 (11)	207 (52)	150 (37)		
Elevated cTnT at baseline	34	7 (21)	3 (9)	24 (71)	2.00 (0.88–4.56)	0.100
Total	435	53 (12)	210 (48)	172 (40)		
Participants without a previous heart disease						
Normal cTnT at baseline	736	52 (7)	498 (68)	186 (25)		
Elevated cTnT at baseline	27	4 (15)	14 (52)	9 (33)	2.20 (0.80–6.06)	0.127
Total	763	56 (7)	512 (67)	195 (26)		

Table 4
Number of participants with normal or elevated levels of N-terminal natriuretic b-type propeptide (proBNP) who had an acute myocardial infarction (AMI), did not have AMI, or deceased of other reasons during the 10-year follow-up period, and hazard ratios (HR) and their 95% confidence intervals (CI) of elevated proBNP for AMI for participants with or without a previous heart disease at baseline.

	n	AMI during the follow-up *n* (%)	No AMI and alive at the end of the follow-up *n* (%)	Deceased of other reasons *n* (%)	HR (95 % CI)	p-value
Participants with a previous heart disease						
Normal proBNP at baseline	299	29 (10)	172 (58)	98 (33)		
Elevated proBNP at baseline	136	24 (18)	38 (28)	74 (54)	1.95 (1.13–3.35)	0.016
Total	435	53 (12)	210 (48)	172 (40)		
Participants without a previous heart disease						
Normal proBNP at baseline	707	47 (7)	488 (69)	172 (24)		
Elevated proBNP at baseline	56	9 (16)	24 (43)	23 (41)	2.54 (1.25–5.17)	0.010
Total	763	56 (7)	512 (67)	195 (26)		

4. Discussion

Comorbidities are especially common among older population, which complicates the definition of reference limits in this population. In accordance with previous studies we found that cTnT and proBNP concentrations are higher also in older population without any cardiac symptoms or diagnosis of a cardiac disease [3,6,20–23,7,9,10,12–15,19]. In our study population the concentrations of cTnT were higher in older men in comparison with older women in all age groups, as most other studies have found as well [6,13,14]. Women had higher concentrations of proBNP as in earlier studies [21–23].

We established reference limits for cTnT and proBNP for older people to help decision-making in clinical settings. Especially the median cTnT values in our population with a previous heart disease were close to the cut-off of 14 ng/L recommended by the manufacturer to rule-out AMI,

even though none had acute symptoms at the time of the initial examination.

There are several threshold levels that are used for proBNP, such as the National Institute for Health and Care Excellence (NICE) guideline of 400 ng/L to rule out HF, and the European Society of Cardiology (ESC) guideline that recommends further investigation at proBNP levels above 125 ng/L [16,27]. According to the manufacturer of the proBNP assay the levels of proBNP rise with increasing age, and in their reference group from the Gutenberg Health study there was a 97.5th percentile value of 879 ng/L for men aged 65–74 years and 623 ng/L for women aged 65–74 years in a population with no prevalent cardiovascular diseases [28].

As TnT and proBNP levels clearly increase with aging, we defined separate reference ranges for age groups 64 to 69-year-olds, 70 to 74-year-olds, 75 to 80-year-olds, and for 80-year-olds and older. The concentrations of both cTnT and proBNP seem to rise with advancing age also after the age of 80 but the dispersion in the population gets larger as seen in Fig. 1. This might be due to more underlying asymptomatic heart conditions in the eldest population even if in our study all participants were carefully examined to exclude all persons with any signs or symptoms of a cardiac disease so that only 60.5 percent of the initial population formed the reference group. The possibility remains that some elderly individuals had asymptomatic cardiac conditions that were not diagnostic at the time of the baseline examination, but these undiagnosed underlying heart conditions were at a stable stage at the time. As this might be a more relevant problem in the eldest group with more dispersion, we suggest using the reference limit of over 80-year-olds for all persons over the age of 80, even if it is likely that the reference limit continues to rise with advancing age.

The application of separate reference limits for older population would have clinical implications, considering the high prevalence of older patients in emergency care as well as in other health care appointments. Troponin levels are often examined with admittance of an elderly person in an emergency room, and it is important to notice that it is quite likely that the person may have a troponin T level higher than the conventional cut-off limit of 14 ng/L also without an acute ischemic disease. When the reference limits that are established for general adult population are used for older people, their higher cTnT and proBNP concentrations may cause overdiagnosis and lead to unnecessary examinations and treatments. In older patients with elevated levels of cTnT, the change in cTnT concentration between two following samples is of clinical significance in acute situations, but less follow-up samples and unnecessary monitoring at emergency care are needed when the initial cut-off limits are more appropriate for the population. Even if follow-up samples are still needed when an elderly person presents with acute cardiac symptoms, it is still important to understand that their baseline cTnT level may be over the conventional cut-off limit unrelated to the acute symptoms.

Even if cTnT is mainly used in acute situations, there is evidence that it also has predictive ability [6,8,9,11]. We studied if elevated cTnT could predict future acute myocardial infarctions in our study participants who already had a diagnosis of a heart disease at baseline. Participants with a heart disease and an elevated cTnT level were more likely to have a new AMI, and only three of those were both alive and did not have a new AMI by the end of the follow-up period. It is nevertheless important to note that most of those who had a new AMI, had a level of cTnT at baseline which was inside our newly established reference limits.

Elevated proBNP level was very common in patients with a previous diagnosis of a heart disease. Elevated levels of proBNP have been shown to predict cardiovascular events and mortality in older with or without heart failure and also after AMI [24,29]. In our study the participants with an elevated level of proBNP were more likely to have an AMI in comparison to participants with a level of proBNP inside the reference limits both among participants with and without a previous diagnosis of a heart disease. The results suggest that levels of both cTnT and proBNP reflect the health status of the heart even when no acute symptoms are present.

There were several limitations in our study. cTnT and proBNP were measured only at one time-point at baseline. The health status of the participants was based on clinical examination by a physician, patient health records and a comprehensive interview but cardiac imaging was not performed for the reference population. We formed the reference population with individuals without symptoms, with no known heart conditions or renal disease. It is also reasonable to assume that potential hidden undiagnosed co-morbidities may impact the reference ranges, and coronary artery disease cannot be excluded without angiographic examination. Increased cTnT levels may be detected in conditions other than acute ischaemia such as inflammation of the heart, endothelial dysfunction, micro-vascular disease or left ventricular strain [5,30].

cTnT presents in different forms in plasma due to its degradation [31]. Intact and long forms of cTnT are detected early after AMI, and truncated smaller fragments of cTnT in myocardial injury attributable to other causes [32]. The heavily truncated fragments may be responsible for chronic cTnT elevations as seen for example in renal dysfunction [33]. The commercial cTnT assay that was used to define cTnT levels in our study measures all forms of cTnT so we could not separate if the participants cTnT elevation was caused by intact or fragmented forms of cTnT [31]. Separation of the different forms of cTnT could have brought more insight on the causes of the elevations of the participants cTnT levels even though participants with a renal dysfunction were not included in the study. We also did not study macrotroponins, which would have resulted in increased concentrations of cTnT.

The data comes from a community-based representative sample of the Finnish older population. The sample size is relatively large, even if the oldest age groups of men and women are smaller which is often a challenge when establishing reference ranges for older population.

5. Conclusions

Our study shows that older population free of heart and kidney diseases have higher levels of cTnT and proBNP than general adult population and thus we suggest using separate reference limits for older population. The new suggested reference limits divided in four age groups for men and women should be validated in another population of older people.

Using these new cut-off limits, elevated proBNP was associated with the occurrence of AMIs in older population with and without a previous diagnosis of a heart disease, and cTnT tended to be associated with their occurrence during a 10-year follow-up period.

CRediT authorship contribution statement

Elisa Heikkilä: . **Taina Katajamäki:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis. **Marika Salminen:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Kerttu Irjala:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Anna Viljanen:** Writing – review & editing, Investigation, Conceptualization. **Marja-Kaisa Koivula:** Writing – review & editing, Investigation. **Kari Pulkki:** Writing – review & editing, Supervision. **Raimo Isoaho:** Writing – review & editing, Conceptualization. **Sirkka-Liisa Kivelä:** Writing – review & editing, Conceptualization. **Matti Viitanen:** Writing – review & editing, Conceptualization. **Minna Löppönen:** Writing – review & editing, Conceptualization. **Tero Vahlberg:** Writing – review & editing, Software, Formal analysis, Conceptualization. **Laura Viikari:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions: Corresponding author had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors (EH, TK, MS, KI, AV, MKK, KP, RI, SLK, MV, ML, TV, and LV) contributed to the study conception and design. Material preparation, data collection and analyses were performed by TK, EH, MS, KI, RI, SLK, ML and TV. The first draft of the manuscript was written by EH, and TK, MS, KI, LV, KP, AV, MKK and TV commented on the manuscript. The authors read and approved the final manuscript.

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