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ORIGINAL RESEARCH

Prognostic Relevance and Lower Limit of the Reference Range of Left Ventricular Global Longitudinal Strain

A Clinical Validation Study

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ABSTRACT

BACKGROUND The lower limit of the reference normal range (LLN) of left ventricular global longitudinal strain (GLS) for each ultrasound software vendor and its prognostic relevance in the elderly and in asymptomatic patients at risk for heart failure (HF) remain uncertain.

OBJECTIVES In this study, the authors sought to validate the LLN of GLS for each ultrasound software vendor and its prognostic relevance in the elderly and in asymptomatic patients at risk for HF.

METHODS To identify the LLN of GLS with the use of 2-dimensional speckle-tracking transthoracic echocardiography, a meta-analysis of studies including healthy subjects was conducted, followed by a validation study in a large cohort of healthy subjects. To validate the prognostic relevance of the LLN of GLS, 2 validation cohort studies were carried out, including elderly subjects aged ≥80 years and asymptomatic ambulatory patients with preserved left ventricular ejection fraction at risk for HF.

RESULTS The meta-analysis, which included 47 studies with a total of 23,208 healthy adult subjects, identified the LLN for GLS at 16% (absolute value) across various ultrasound software vendors, including EchoPac, TomTec, and QLab. In the validation cohort study, which included 2,217 healthy adult subjects, a GLS cutoff of 16% was also identified as the LLN. Concerning the prognostic relevance of the LLN of GLS, a value of GLS <16% was significantly associated with HF hospitalization in asymptomatic ambulatory patients at risk for HF (n = 667; OR within 6 years: 5.1 [95% CI: 1.5-17.0]) and in elderly subjects (n = 159; OR within 2 years: 3.1 [95% CI: 1.1-8.8]).

CONCLUSIONS This clinical validation study provides important clinical data concerning the LLN of GLS (identified and validated at 16%) and its prognostic relevance in the elderly and in asymptomatic ambulatory patients at risk for HF. (JACC Cardiovasc Imaging. 2025;18:525-536) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

GLS = global longitudinal strain

HF = heart failure

LLN = lower limit of the reference normal range

LV = left ventricular

Two-dimensional (2D) left ventricular (LV) global longitudinal systolic strain (GLS), with the use of 2D transthoracic speckle-tracking echocardiography (STE), is a sensitive parameter for detecting early or subclinical LV systolic dysfunction, even when left ventricular ejection fraction (LVEF) is preserved.[1-3] However, some important issues concerning GLS remain uncertain, such as the cutoff of the lower limit of the reference normal range (LLN) of GLS for each ultrasound software vendor and its prognostic relevance in the elderly and in asymptomatic ambulatory patients at risk for heart failure (HF).

Although previous meta-analyses have been carried out to identify the normal range of GLS,[4-6] the specific cutoff of the LLN of GLS for each software vendor remains undefined. In addition, clinical validation of the prognostic relevance of the LLN of GLS in elderly subjects ≥80 years and in asymptomatic ambulatory patients with preserved LVEF at risk for HF has not been extensively studied. Therefore, the purposes of the present study were: 1) to identify the LLN of GLS for each ultrasound software vendor; and 2) to validate the prognostic relevance of the LLN of GLS in the elderly and in asymptomatic ambulatory patients with preserved LVEF at risk for HF.

METHODS

META-ANALYSIS OF THE LLN OF GLS. A conventional meta-analysis (ie, a nonindividual participant data meta-analysis) was performed, including studies in the English language indexed in PubMed that analyzed GLS (≥16 LV segments) with the use of 2DSTE in healthy adult subjects (≥18 years of age). Studies with a sample size of <120 healthy adult subjects were excluded to avoid biases linked to a small size when determining the LLN.[7-9] The search process was focused on studies that had been published after the 2015 joint EACVI (European Association of Cardiovascular Imaging)/ASE (American Society of Echocardiography) Industry Task Force for LV strain standardization[10] to avoid biases linked to potential differences in LV strain analyses between old and new software and to include contemporary ultrasound software packages used to analyze GLS. The search process was completed on June 1, 2024. The methodologic description of the meta-analysis was registered and published in detail in a prespecified protocol (CRD42018104096).[11]

VALIDATION OF THE LLN OF GLS IN A LARGE COHORT OF HEALTHY ADULT SUBJECTS. With the purpose of validating the LLN of GLS found in the meta-analysis, a validation cohort study on a large cohort of healthy adult subjects (sample size >2,000) was performed (**Figure 1**). A cohort of healthy adult subjects with preserved LVEF (women: LVEF ≥54%; men: LVEF ≥52%) included in a cardiovascular health screening program at the MacKay Memorial Hospital was analyzed.[12] This cohort comprised healthy adult subjects without arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, coronary artery disease, or an estimated glomerular filtration rate <60 mL/min/1.73 m^2. GLS was determined as the average of the GLS values from the apical 4-, 2-, and 3-chamber views (analyzing 6 LV segments in each view) using a mid-myocardial strain analysis with the EchoPac software vendor (version 113, GE Vingmed Ultrasound; GE HealthCare). The Institutional Review Board approved the data analysis, and informed consent was obtained from all subjects.

VALIDATION OF THE PROGNOSTIC RELEVANCE OF THE LLN OF GLS IN THE ELDERLY AND IN ASYMPTOMATIC PATIENTS AT RISK FOR HF. To validate the prognostic relevance of the LLN of GLS in the elderly and in asymptomatic ambulatory patients at risk for HF, 2 cohorts composed of elderly subjects ≥80 years and asymptomatic ambulatory patients with cardiovascular (CV) risk factors (arterial hypertension, diabetes mellitus, or history of coronary artery disease) and preserved LVEF (women: LVEF ≥ 54%; men: LVEF ≥ 52%) were analyzed (**Figure 1**). The subjects of the elderly cohort were part of previous studies conducted by the authors at the Charite, Copenhagen, Leuven, Rennes, Wroclaw, and Taipei (MacKay) University Hospitals[12-17] and were included in the current validation study if they had a preserved LVEF. Regarding the cohort of asymptomatic ambulatory patients at risk for HF, these patients were included from a cardiovascular health screening program at the MacKay Memorial Hospital.[12] In both cohorts, patients with atrial fibrillation, severe valvular heart

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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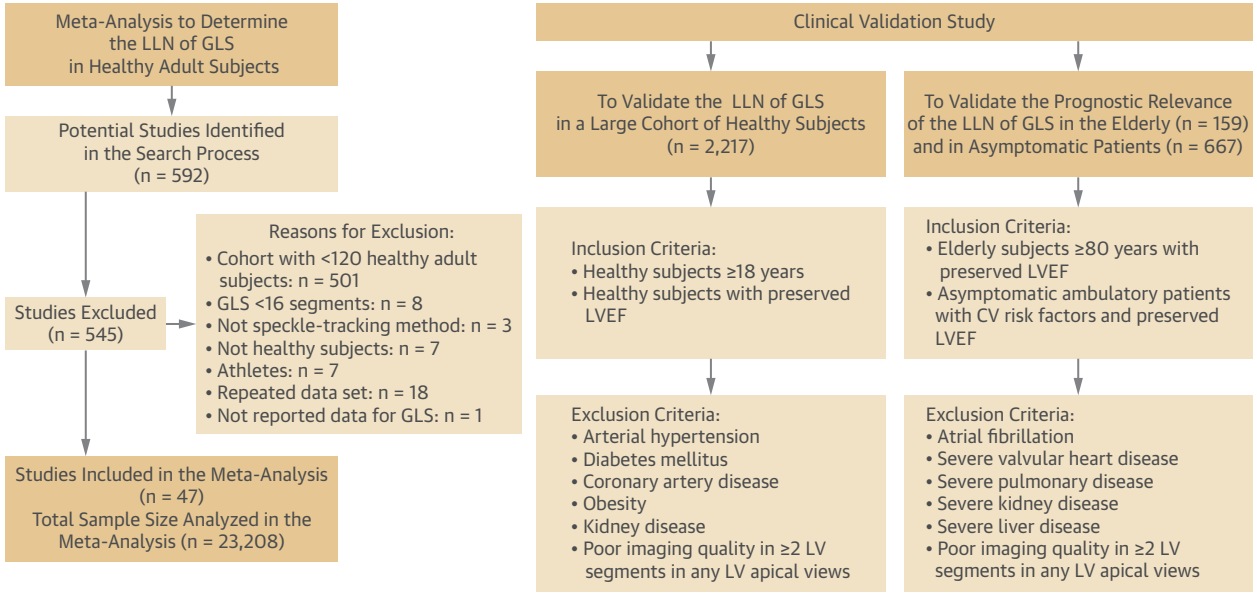
FIGURE 1 Flow Diagram of the Meta-Analysis and the Clinical Validation Study



CV = cardiovascular; GLS = global longitudinal strain; LLN = lower limit of the reference normal range; LV = left ventricular; LVEF = left ventricular ejection fraction.

disease, or severe pulmonary, kidney, or liver disease, and patients with poor imaging quality in ≥2 LV segments in any LV apical view were excluded. GLS was determined as the average of the GLS values from the apical 4-, 2-, and 3-chamber views (analyzing 6 LV segments in each view) using a mid-myocardial strain analysis with the EchoPac software vendor (version 113, GE Vingmed Ultrasound).

The prognostic relevance of the LLN of GLS was determined by analyzing the risk for HF hospitalization, which was defined as HF hospitalization due to acute or decompensated HF. The follow-up and HF events were determined by a sequential regular visit (biennially) and by analyzing the digital medical records. For the elderly cohort, the risk of HF was analyzed over a period of 2 years. In contrast, for the cohort of asymptomatic ambulatory patients with CV risk factors and preserved LVEF, the risk of HF was analyzed over a period of 6 years. This distinction was made in consideration of the shorter life expectancy of elderly subjects ≥80 years compared with asymptomatic ambulatory patients with CV risk factors and preserved LVEF whose average age is around 60 years. The Institutional Review Boards approved the analysis of the data, and informed consent was obtained from all subjects.

BIAS ASSESSMENTS AND STATISTICAL ANALYSES. In accordance with the recommendations stated in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[18] and according to a prespecified protocol for the meta-analysis (CRD42018104096),[11] the following tools were applied to reduce biases and increase the accuracy of the findings of the meta-analysis: 1) studies with sample sizes of <120 healthy adult subjects were excluded to avoid biases linked to small sample size when determining the LLN;[7-9] 2) the calculation of the pooled LLN of GLS for a specific software vendor was avoided when only 1 study for the specific software vendor was published; 3) heterogeneity between studies was analyzed with the use of Cochran's *Q* test (*Q*) and I^2 statistic test (I^2) (statistical heterogeneity was not evaluated when fewer than 10 studies were included in the meta-analysis to avoid potential biases associated with *Q* and I^2 test analyses);[19]

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4) publication biases were assessed by means of Egger and Begg tests; 5) the quality of the included studies was evaluated taking into account the description of clinical and cardiac characteristics of the cohort included as well as the report of the intra- and inter-observer reproducibility of GLS; 6) analysis of subgroups (sex and age) were performed only in studies with adequate sample size in the subgroup analyzed (ie, ≥120 healthy adult subjects for each subgroup);[7-9] and 7) in accordance with the ASE/EACVI task force for LV strain standardization, clinically relevant differences in the LLN of GLS between software vendors, as well as between clinical subgroups such as women and men, and younger and older subjects (<60 and ≥60 years), were defined as relative differences >10% in the LLN of GLS.[20,21]

Following the recommendations of the ASE and EACVI for chamber quantification,[1] and given that GLS typically has a normal distribution in healthy adult subjects, a standard calculation of the LLN for GLS was performed (ie, −1.96 SD from the arithmetic mean).[1,7-9] Nonetheless, if studies reported a non-normal distribution of GLS data, the 2.5th percentile was used to determine the LLN of GLS,[1,7-9] and this methodology was indicated when applied. The LLN of GLS and its 95% CI (±1.96 SE) was determined for each study, and then the pooled LLN of GLS from all studies for each software vendor was calculated. The SE of the LLN of GLS from each study was calculated as the square root of ($3 \times SD^2$)/sample size.[22] For the meta-analysis, the generic inverse variance method was used to determine the pooled LLN of GLS and its 95% CI,[19] and a random-effect model was selected to avoid bias if the data had significant heterogeneity.[19] Nonetheless, a fixed-effect model was selected if it was not possible to evaluate heterogeneity between studies (ie, <10 studies included in the meta-analysis).[19]

Continuous data were presented as mean ± SD and dichotomous data in percentage. Values of GLS were reported as absolute values. In the healthy validation cohort, the LLN of GLS was calculated as −1.96 SD from the arithmetic mean, given that the data followed a normal distribution. In addition, a robust and standard statistical validation method (ie, bootstrapping analysis)[8] was performed to determine and validate the LLN of GLS. Specifically, a random bootstrapping analysis with 100,000 replications of the sample was conducted on the data from the healthy validation cohort. In the prognostic validation cohorts of elderly individuals and patients at risk for HF, the association between the LLN of GLS and outcomes was analyzed with the use of logistic regression analysis, with the OR as the primary measure. Differences were considered to be statistically significant when the value of $P < 0.05$. MedCalc statistical software (version 23.0) was used to analyze the data.

RESULTS

META-ANALYSIS OF THE LLN OF GLS. The LLN of GLS (by default strain analysis) for the software vendors EchoPac (GE Vingmed Ultrasound), TomTec (TomTec), and QLab (Philips) was 16% (absolute value) (**Tables 1 and 2**, Supplemental Figures 1 to 6). Regarding the specific myocardial layer for strain analysis, the LLN of GLS for EchoPac using the standard or by default GLS analysis (ie, mid-myocardial layer) was 16%, whereas the LLN of GLS for EchoPac analyzing the endocardial layer was 19% (**Table 1**). For the TomTec (package 2D CPA) and QLab (package aCMQ) software vendors, the LLN of GLS using the standard or by default GLS analysis (ie, endocardial layer) was 16% for both (**Table 2**), and only 2 studies were published using the mid-myocardial layer with these software vendors in a large cohort of healthy adult subjects (ie, sample size ≥120) (Supplemental Table 1). The data or number of studies including large cohorts of healthy adult subjects (ie, sample size ≥120) was small (ie, only 1 study) for software vendors such as Toshiba/Canon UltraExtend, Siemens Syngo-VVI, Mindray, and Us2.ai, and even nonexistent (ie, no study) for vendors such as Epsilon, Esaote 2D X-Strain, Hitachi, Samsung, Ultromics, and DiA Imaging Analysis. These limited data introduced bias and did not allow for the calculation of the definitive LLN of GLS for these ultrasound software vendors (Supplemental Table 2). Regarding subgroup analysis by sex and age, there were no clinically relevant differences (ie, ≤10% relative differences or ≤1 strain unit) in the LLN of GLS between women and men or between younger and older subjects (Supplemental Tables 3 and 4). However, for most software vendors (with the exception of EchoPac), the number of studies that included large cohorts of ≥120 healthy subjects

TABLE 1 Meta-Analysis of the LLN of GLS Using the EchoPac Software Vendor

First Author, Year[a]	Sample Size	Age, y	Women, n	Country	Software Package	GLS, %	LLN, %	Layer
Morris et al, 2015[b,S1]	148	34 ± 12	87	Germany	EchoPac (v113)	20.5 ± 2.2	16.1	Mid
Barbier et al, 2015[b,S2]	131	42 ± 15	32	Italy	EchoPac (v12)	21.2 ± 2.4	16.4	Mid
Jensen et al, 2015[S3]	198	48 ± 14	95	Denmark	EchoPac (v10)	18.8 ± 2.5	13.9	Mid
Kuznetsova et al, 2016[b,S4]	207	47 ± 14	111	Belgium	EchoPac (v113)	21.2 ± 1.6	18.0	Mid
Christiansen et al, 2016[S5]	180	32 ± 8	88	Norway	EchoPac (v12)	21.4 ± 2.0	17.4	Mid
Khamis et al, 2016[S6]	410	22-82	n/a	Israel and Germany	EchoPac (v113)	21.3 ± 2.8	15.8	Mid
Park et al, 2016[S7]	501	47 ± 15	265	South Korea	EchoPac (v201)	20.4 ± 2.2	16.0	Mid
Nagata et al, 2017[S8]	235	45 ± 14	118	Japan	EchoPac (v113)	20.0 ± 2.0	16.0	Mid
Schröder et al, 2017[S9]	199	44 ± 5	58	Germany	EchoPac (v113)	26.0 ± 3.0	20.1	Mid
Lai et al, 2017[b,S10]	2,798	47 ± 9	1,041	Taiwan	EchoPac (v10)	20.3 ± 1.8	16.7	Mid
Alcidi et al, 2018[S11]	266	39 ± 17	137	Italy	EchoPac (v201)	22.7 ± 1.8	19.1	Mid
Aurich et al, 2018[S12]	202	51-67	48	Germany	EchoPac (v10)	19.5 ± 1.7	16.1	Mid
Brand et al, 2018[b,S13]	190	33 ± 12	190	Germany	EchoPac (v113)	21.3 ± 2.1	17.1	Mid
Bogunovic et al, 2018[S14]	131	42 ± 10	65	Germany	EchoPac (v113)	21.2 ± 3.3	14.7	Mid
Zhang et al, 2018[S15]	147	54 ± 11	147	United Kingdom	EchoPac (v10)	21.5 ± 1.6	18.3	Mid
Ikonomidis et al, 2018[S16]	160	48 ± 13	54	Greece	EchoPac (v n/a)	21.9 ± 1.5	18.9	Mid
Morbach et al, 2019[b,S17]	323	49 ± 11	177	Germany	EchoPac (v113)	19.7 ± 2.2	15.3	Mid
Aagaard et al, 2020[b,S18]	594	63 ± 0.6	321	Norway	EchoPac (v201)	20.7 ± 2.2	16.3	Mid
Rimbaş et al, 2020[S19]	151	51 ± 14	82	Romania and Italy	EchoPac (v113)	20.9 ± 2.5	16.0	Mid
Tsugu et al, 2020[S20]	287	46 ± 14	178	Europe	EchoPac (v203)	21.5 ± 2.2	17.1	Mid
d'Andrea et al, 2020[S21]	150	32 ± 5	65	Italy	EchoPac (v202)	22.4 ± 3.3	15.9	Mid
Verdugo-Marchese et al, 2020[b,S22]	907	46 ± 13	482	France	EchoPac (v10)	21.1 ± 2.5	16.2	Mid
Sengupta et al, 2021[b,S23]	880	39 ± 12	319	India	EchoPac (v202)	21.0 ± 2.9	15.3	Mid
Stefani et al, 2021[S24]	147	44 ± 14	69	Australia	EchoPac (v203)	19.3 ± 2.4	14.5	Mid
Wang et al, 2021[b,S25]	157	45 ± 13	86	China	EchoPac (v202)	20.6 ± 2.8	15.1	Mid
Wegener et al, 2021[b,S26]	290	37 ± 14	174	Brazil	EchoPac (v113)	19.8 ± 2.1	15.6	Mid
Skaarup et al, 2022[S27]	1,905	46 ± 15	1,176	Denmark	EchoPac (v113)	19.9 ± 2.1	15.7	Mid
d'Andrea et al, 2022[S28]	180	32 ± 4	78	Italy	EchoPac (v202)	21.9 ± 3.8	14.4	Mid
Kornev et al, 2022[S29]	407	53 ± 8	250	Norway and Russia	EchoPac (v203)	20.8 ± 2.3	16.2	Mid
Nyberg et al, 2023[b,S30]	1,194	57 ± 12	662	Norway	EchoPac (v204)	19.8 ± 2.1	15.6	Mid
Grönlund et al, 2024[S31]	405	46 ± 0	232	Finland	EchoPac (v n/a)	21.1 ± 2.5	16.2	Mid
Moraru et al, 2024[S32]	200	37 ± 11	70	Romania	EchoPac (v204)	20.0 ± 2.4	15.2	Mid
Results of the meta-analysis for the LLN of GLS in the mid-myocardial layer using the EchoPac software vendor: Total sample size (n = 14,280) Pooled LLN of GLS: 16.3% (95% CI: 16.0%-16.7%)								
Khamis et al, 2016[b,S6]	410	22-82	n/a	Israel and Germany	EchoPac (v113)	24.4 ± 3.2	18.1	Endo
Nagata et al, 2017[b,S8]	235	45 ± 14	118	Japan	EchoPac (v113)	23.1 ± 2.3	18.5	Endo
Schröder et al, 2017[S9]	199	44 ± 5	58	Germany	EchoPac (v113)	32.0 ± 4.0	24.1	Endo
Alcidi et al, 2018[S11]	266	39 ± 17	137	Italy	EchoPac (v201)	25.4 ± 2.1	21.2	Endo
Rimbaş et al, 2020[S19]	151	51 ± 14	82	Romania and Italy	EchoPac (v113)	23.4 ± 2.9	17.7	Endo
Tsugu et al, 2020[S20]	287	46 ± 14	178	Europe	EchoPac (v203)	24.1 ± 2.4	19.3	Endo
Verdugo-Marchese et al, 2020[b,S22]	907	46 ± 13	482	France	EchoPac (v10)	23.4 ± 2.6	18.3	Endo
Skaarup et al, 2022[S27]	1,905	46 ± 15	1,176	Denmark	EchoPac (v113)	23.5 ± 2.5	18.6	Endo
Kornev et al, 2022[S29]	407	53 ± 8	250	Norway and Russia	EchoPac (v203)	24.0 ± 2.7	18.7	Endo
Moraru et al, 2024[S32]	200	37 ± 11	70	Romania	EchoPac (v204)	22.9 ± 2.7	17.6	Endo
Results of the meta-analysis for the LLN of GLS in the endocardial layer using the EchoPac software vendor: Total sample size (n = 4,967) Pooled LLN of GLS: 19.2% (95% CI: 18.4%-19.9%)								

Values are mean ± SD, unless otherwise indicated. [a]See the Supplemental References for the references of these studies (S1 to S32). [b]Requested data. GLS is the average of the peak negative systolic longitudinal strain obtained from the apical 4-, 2-, and 3-chamber views (analyzing 6 LV segments in each view) using 2D speckle-tracking echocardiography.

2D = 2-dimensional; GLS = global longitudinal strain; LLN = lower limit of the reference normal range; LV = left ventricular; n/a = not applicable.

TABLE 2 Meta-Analysis of the LLN of GLS Using the QLab and TomTec Software Vendors

First Author, Year[a]	Sample Size	Age, y	Women, n	Country	Software Package	GLS, %	LLN, %	Layer
Menting et al, 2016[b,S33]	141	44 ± 13	74	Netherlands	QLab (aCMQ)	20.8 ± 2.0	16.8	Endo
Yaan et al, 2018[S34]	180	58 ± 8	76	Turkey	QLab (aCMQ)	19.6 ± 3.0	13.7	Endo
Yaman et al, 2018[S34]	128	56 ± 8	75	Turkey	QLab (aCMQ)	20.9 ± 2.3	16.3	Endo
Sullere et al, 2018[b,S35]	707	40 ± 11	263	India	QLab (aCMQ)	20.0 ± 2.2	15.6	Endo
Wang et al, 2021[b,S36]	414	47 ± 15	300	China	QLab (aCMQ)	22.1 ± 1.9	18.3	Endo
Peng et al, 2023[S37]	152	40 ± 11	99	China	QLab (aCMQ)	20.8 ± 2.4	16.0	Endo
Wang et al, 2024[b,S38]	1,683	45 ± 14	964	China	QLab (aCMQ)	19.8 ± 2.2	15.4	Endo
Results of the meta-analysis for the LLN of GLS using the QLab (aCMQ) software vendor: Total sample size (n = 3,405) Pooled LLN of GLS (endocardial): 16.0% (95% CI: 15.9%-16.1%)								
Sugimoto et al, 2017[S39]	549	45 ± 13	322	Europe and USA	TomTec (2D CPA)	22.5 ± 2.7	17.2	Endo
Yoshida et al, 2019[b,S40]	481	60 ± 12	260	Japan	TomTec (2D CPA)	22.0 ± 2.9	16.3	Endo
Perry et al, 2020[b,S41]	200	47 ± 13	71	Australia	TomTec (2D CPA)	20.4 ± 3.2	14.1	Endo
Faganello et al, 2020[S42]	176	47 ± 18	89	Italy	TomTec (2D CPA)	24.0 ± 2.7	18.7	Endo
Mutluer et al, 2020[b,S43]	130	45 ± 14	65	Netherlands	TomTec (2D CPA)	20.2 ± 2.1	16.0	Endo
Ferrara et al, 2021[S44]	269	43 ± 14	146	Italy	TomTec (2D CPA)	23.1 ± 2.5	18.2	Endo
Pugliese et al, 2022[S45]	155	65 ± 11	62	Italy	TomTec (2D CPA)	18.7 ± 2.3	14.1	Endo
Singulane et al, 2022[S46]	1,572	47 ± 17	763	Mixed	TomTec (2D CPA)	21.3 ± 2.1	17.1	Endo
Chen et al, 2023[S47]	156	42 ± 13	90	Australia	TomTec (2D CPA)	21.0 ± 2.0	17.0	Endo
Results of the meta-analysis for the LLN of GLS using the TomTec (2D CPA) software vendor: Total sample size (n = 3,688) Pooled LLN of GLS (endocardial): 16.9% (95% CI: 16.8%-17.0%)								
Peng et al, 2023[S37]	152	40 ± 11	99	China	AutoStrain[c] (QLab/TomTec)	21.0 ± 2.5	16.1	Endo
Wang et al, 2024[b,S38]	1,683	45 ± 14	964	China	AutoStrain[c] (QLab/TomTec)	21.4 ± 2.8	15.9	Endo
Results of the meta-analysis for the LLN of GLS using the AutoStrain (TomTec/QLab) software vendor: Total sample size (n = 1,835) Pooled LLN of GLS (endocardial): 16.0% (95% CI: 15.9%-16.1%)								

Values are mean ± SD, unless otherwise indicated. [a]See the Supplemental References for the references of these studies (S33 to S47). [b]Requested data. [c]The AutoStrain software is the automatic measurement package of GLS from TomTec software vendor, which is also incorporated as an option in the new software versions (so far, versions 12 and 13) of the QLab software from the Phillips vendor. This optional automatic measurement package (AutoStrain) for GLS from TomTec, also incorporated in newer versions of QLab, is different (ie, uses a different algorithm to calculate GLS) from the standard strain analysis provided by TomTec (ie, 2D CPA) and QLab (ie, aCMQ). For a detailed description of the standard or default GLS analysis across different software vendors, see the Supplemental Methods.

2D CPA = 2-dimensional cardiac performance analysis software package from the TomTec software vendor; aCMQ = automated cardiac motion quantification software package from QLab; other abbreviations as in Table 1.

aged ≥60 years was very small (<2), which limited and biased the comparison of the LLN of GLS between younger and older subjects.

The studies included in the meta-analysis were of adequate quality, exhibited no significant publication bias, and showed heterogeneity attributable to variations in sample size (Supplemental Figures 1 to 6, Supplemental Table 5).

VALIDATION AND TEST OF THE LLN OF GLS IN A LARGE COHORT OF HEALTHY ADULT SUBJECTS. In a validation cohort study that included 2,217 healthy adult subjects, results similar to those of the meta-analysis were observed. In this respect, the LLN of GLS was 16% in the healthy validation cohort (Table 3), which was further validated through a random bootstrapping analysis using 100,000 replications of the sample (yielding an LLN of GLS of 16.6% [95% CI: 16.5%-16.7%]). Regarding subgroup analysis by sex and age, there were no clinically relevant differences (ie, ≤10% relative differences or ≤1 strain unit) in the LLN of GLS between women and men and between younger and older subjects (Table 3). Furthermore, when analyzing the proportion of healthy subjects with GLS values <16%, fewer than 2% of the healthy cohort had values below this threshold (Table 3). This proportion was consistent across women, men, and older subjects (Table 3).

PROGNOSTIC RELEVANCE OF THE LLN OF GLS IN THE ELDERLY AND IN ASYMPTOMATIC PATIENTS AT RISK FOR HF. To validate the prognostic relevance of the LLN of GLS in the elderly and in

TABLE 3 Clinical Validation Cohort Study to Validate the LLN of GLS

Characteristics of the healthy cohort	
Age, y	47 ± 10
Women	36.7
Body mass index, kg/m^2	23.4 ± 2.2
Sinus rhythm	100
Arterial hypertension	0
Diabetes mellitus	0
History of coronary artery disease	0
LVEF, %	62.9 ± 5.7
LVEF <50%	0
Validation of the LLN of GLS	
Whole cohort (n = 2,217)	
GLS, %	20.4 ± 1.9
LLN of GLS, %	16.6 (16.4-16.7)
Rate of healthy subjects with GLS <16%	0.7
Men (n = 1,403)	
GLS, %	19.9 ± 1.7
LLN of GLS, %	16.5 (16.3-16.6)
Rate of healthy men with GLS <16%	0.9
Women (n = 814)	
GLS, %	21.2 ± 1.9
LLN of GLS, %	17.4 (17.1-17.6)
Rate of healthy women with GLS <16%	0.4
<60 y (n = 1,968)	
GLS, %	20.4 ± 1.8
LLN of GLS, %	16.8 (16.6-16.9)
Rate of healthy subjects <60 y with GLS <16%	0.6
≥60 y (n = 249)	
GLS, %	20.2 ± 2.0
LLN of GLS, %	16.2 (15.8-16.6)
Rate of healthy subjects ≥60 y with GLS <16%	1.6

Values are mean ± SD, %, or (95% CI). GLS values are shown as absolute values. GLS was analyzed using the EchoPac software vendor.

Abbreviations as in Table 1.

TABLE 4 Clinical Validation Cohort Study to Validate the Prognostic Relevance of the LLN of GLS in the Elderly (≥80 Years) and in Asymptomatic Patients at Risk for HF

	Cohort at Risk for HF (n = 667)	Elderly Cohort (n = 159)
Age, y	57 ± 10	84 ± 3
Women	32.7	57.2
Sinus rhythm	100	100
Arterial hypertension	78.8	94.9
Diabetes mellitus	34.0	27.0
History of coronary artery disease	5.3	33.9
LVEF, %	63.3 ± 5.6	62.8 ± 5.7
LVEF <50%	0	0
GLS, %	19.6 ± 1.9	18.7 ± 3.0
Period with complete follow-up, y	6	2
HF hospitalization (number of events during follow-up)[a]	51	19
Validation of the prognostic relevance of the LLN of GLS (ie, GLS <16%)		
Risk for HF hospitalization: GLS <16%	5.1 (1.5-17.0)	3.1 (1.1-8.8)
Rate of HF hospitalization: GLS <16% vs ≥16%	28.5 vs 7.1; $P < 0.01$	24.1 vs 9.2; $P = 0.02$
Analysis in the subgroup of women		
Risk for HF hospitalization: GLS <16%	10.1 (1.9-53.8)	6.8 (1.7-25.8)
Rate of HF hospitalization: GLS <16% vs ≥16%	50.0 vs 8.9; $P < 0.01$	33.3 vs 6.8; $P < 0.01$

Values are mean ± SD, %, or OR (95% CI), unless otherwise indicated. GLS values are shown as absolute values. GLS was analyzed using the EchoPac software vendor. [a]HF hospitalization was analyzed over a period of 6 years in the asymptomatic cohort at risk for HF and over a period of 2 years in the elderly cohort.

Abbreviations as in Table 1.

asymptomatic patients at risk for HF, a cohort of 159 elderly subjects aged ≥80 years and a cohort of 667 asymptomatic ambulatory patients with CV risk factors and preserved LVEF were analyzed (Figure 1, Table 4). In this respect, a GLS value <16% was significantly associated with an increased risk of HF hospitalization in the cohort of elderly subjects (OR within 2 years: 3.1 [95% CI: 1.1-8.8]) and in the cohort of asymptomatic patients at risk for HF (OR within 6 years: 5.1 [95% CI: 1.5-17.0]) (Table 4, Figure 2). Moreover, an abnormal value of GLS (ie, <16%) provided incremental prognostic relevance over abnormal values of standard echocardiographic parameters, such as tricuspid regurgitation (TR) velocity, maximal left atrial volume index (LAVI), and mitral E/e′ average septal-lateral ratio (average E/e′), in the cohort of elderly subjects and in the cohort of asymptomatic patients at risk for HF (Figure 3, Supplemental Figure 7).

DISCUSSION

This clinical validation study, which initially involved a meta-analysis of 23,208 healthy adult subjects, followed by a large validation study including 2,217 healthy subjects, 667 asymptomatic patients, and 159 elderly subjects aged ≥80 years, provides important clinical data regarding the LLN for GLS (identified and validated as 16%) and its prognostic relevance (increased risk for HF hospitalization) in elderly individuals and in asymptomatic patients at risk for HF.

RELEVANCE OF KNOWING THE LLN OF GLS. In clinical practice and research, knowing the specific cutoff that defines normal or abnormal cardiac function is crucial for clinical decision making and for interpreting the results of clinical studies or trials.[1,23]

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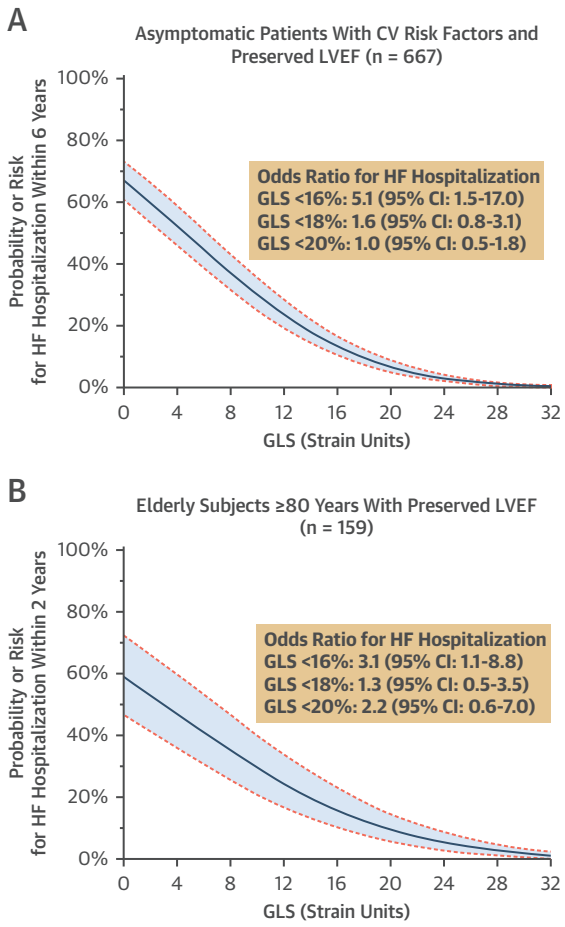
FIGURE 2 Association of GLS Worsening With HF Hospitalization



Association of GLS worsening with HF hospitalization (A) in asymptomatic patients at risk for HF and (B) in the elderly (≥80 years of age). Note the significantly higher risk for HF hospitalization when GLS is <16% (OR: 5.1 [95% CI: 1.5-17.0] and OR: 3.1 [95% CI: 1.1-8.8], respectively; $P < 0.05$; statistical power: >80%). GLS values are shown as absolute values. See Table 4 for patient characteristics. HF = heart failure; other abbreviations as in Figure 1.

For conventional LV parameters such as LVEF, there is a well validated cutoff that defines normal or abnormal LV systolic function.[1,23] However, some important issues remain concerning GLS, such as the lack of a validated cutoff to determine normal or abnormal LV systolic function and the uncertainty of whether this GLS cutoff might vary between ultrasound software vendors.

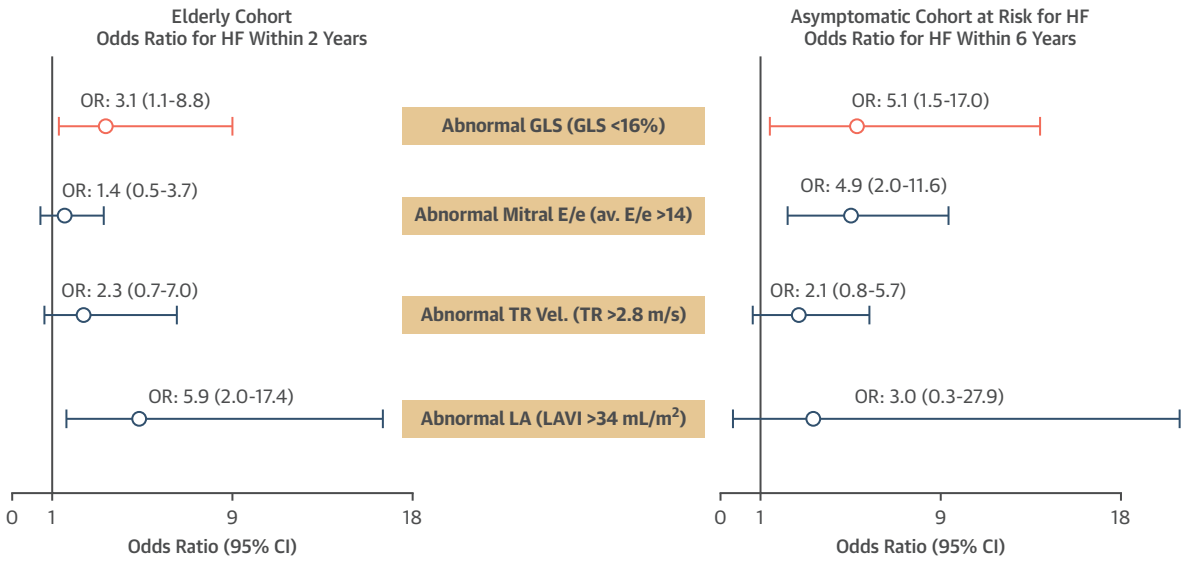
In the present clinical validation study, we first conducted a meta-analysis including 23,208 healthy adult subjects, and the LLN of GLS for the most commonly used ultrasound software vendors (ie, EchoPac, TomTec, and QLab) was 16%, which was consistent with the findings from the large healthy validation cohort including 2,217 healthy adult subjects. Regarding the specific myocardial layer analyzed, the LLN of GLS for EchoPac using the standard or default GLS analysis (ie, mid-myocardial layer) was 16%, whereas the LLN of GLS for EchoPac analyzing the endocardial layer was 19%, a difference that is clinically significant and should be considered when reporting GLS values in clinical practice and research.

PROGNOSTIC RELEVANCE OF THE LLN OF GLS IN THE ELDERLY AND IN ASYMPTOMATIC PATIENTS AT RISK FOR HF. Previous studies using different cutoffs of GLS have evaluated the potential prognostic relevance of GLS in determining the risk of CV outcomes in diverse and heterogeneous populations of patients with CV diseases.[24-34] However, some of these studies used continuous Cox regression analyses without providing the specific cutoff of GLS associated with worse CV outcomes.[24,25] Moreover, other studies have proposed potential specific cutoffs for GLS linked to worse outcomes, but those cutoffs were within the normal range of GLS (ie, ≥16%),[26,27] which renders the outcome analysis inaccurate, because it is not expected that a normal value of any cardiac parameter would be associated with worse CV outcomes. Furthermore, the prognostic relevance of an abnormal GLS (ie, <16%) in asymptomatic patients at risk for HF has been analyzed in only a few studies,[35-37] and it remains uncertain in elderly subjects aged ≥80 years.

In this context, the present clinical validation cohort study analyzed the prognostic relevance of the LLN of GLS on 2 large cohorts, involving elderly subjects ≥80 years and asymptomatic ambulatory patients with preserved LVEF at risk for HF. We found that a value of GLS <16% was significantly associated with an increased risk of HF hospitalization within 2 and 6 years, respectively. Furthermore, an abnormal value of GLS provided incremental prognostic relevance over abnormal values of standard echocardiographic parameters such as TR velocity, LAVI, and mitral average E/e′. Thus, these findings highlight the importance of an accurate definition of abnormal GLS to better identify patients with preserved LVEF who are at higher risk for HF.

STUDY LIMITATIONS. Some limitations should be considered when interpreting the results of this clinical validation study. First, regarding the meta-analysis, the number of studies that included large

FIGURE 3 **Incremental Prognostic Relevance of Abnormal GLS Over Standard Parameters in Predicting the Risk of HF Hospitalization in the Elderly (≥80 Years) and in Asymptomatic Patients at Risk for HF**



See Table 4 for patient characteristics. LAVI = left atrial volume index; TR = tricuspid regurgitation; other abbreviations as in Figures 1 and 2.

cohorts of healthy adult subjects (ie, sample size ≥120) was small (only 1 study) for certain software vendors, such as Toshiba/Canon UltraExtend, Siemens Syngo-VVI, Mindray, and Us2.ai, or even nonexistent (no study) for vendors such as Epsilon, Esaote 2D X-Strain, Hitachi, Samsung, Ultromics, and DiA Imaging Analysis. This limitation introduced bias and prevented the calculation of a definitive LLN of GLS for those software vendors. Therefore, further large studies in healthy adult subjects are necessary to define the LLN of GLS for those ultrasound software vendors.

Second, for most software vendors (except EchoPac), the number of studies that included large cohorts with ≥120 healthy older subjects aged ≥60 years was small (<2 studies), limiting the comparison of the LLN of GLS between younger and older subjects for vendors other than EchoPac. Similarly, in the present clinical validation study, the sample size of elderly subjects aged ≥80 years was modest (n = 159). Therefore, larger studies are needed to validate the prognostic relevance of abnormal GLS (ie, <16%) in elderly subjects aged ≥80 years.

Third, although the prognostic role of the LLN of GLS was analyzed in a large cohort of asymptomatic patients with CV risk factors (n = 659), it is important to note that patients with atrial fibrillation, severe valvular heart disease, and reduced LVEF were excluded from that cohort. Therefore, the findings of this study should be applied and extrapolated only to the specific cohort studied (ie, asymptomatic ambulatory patients with CV risk factors, preserved LVEF, sinus rhythm, and no severe valvular heart disease).

CONCLUSIONS

The present clinical validation study (Central Illustration), which first performed a meta-analysis of 23,208 healthy adult subjects and then conducted a large validation study including 2,217 healthy subjects, 667 asymptomatic patients, and 159 elderly subjects ≥80 years, provides important clinical data concerning the LLN of GLS (identified and validated as 16%) and its prognostic relevance in the elderly and in asymptomatic patients with preserved LVEF at risk for HF.

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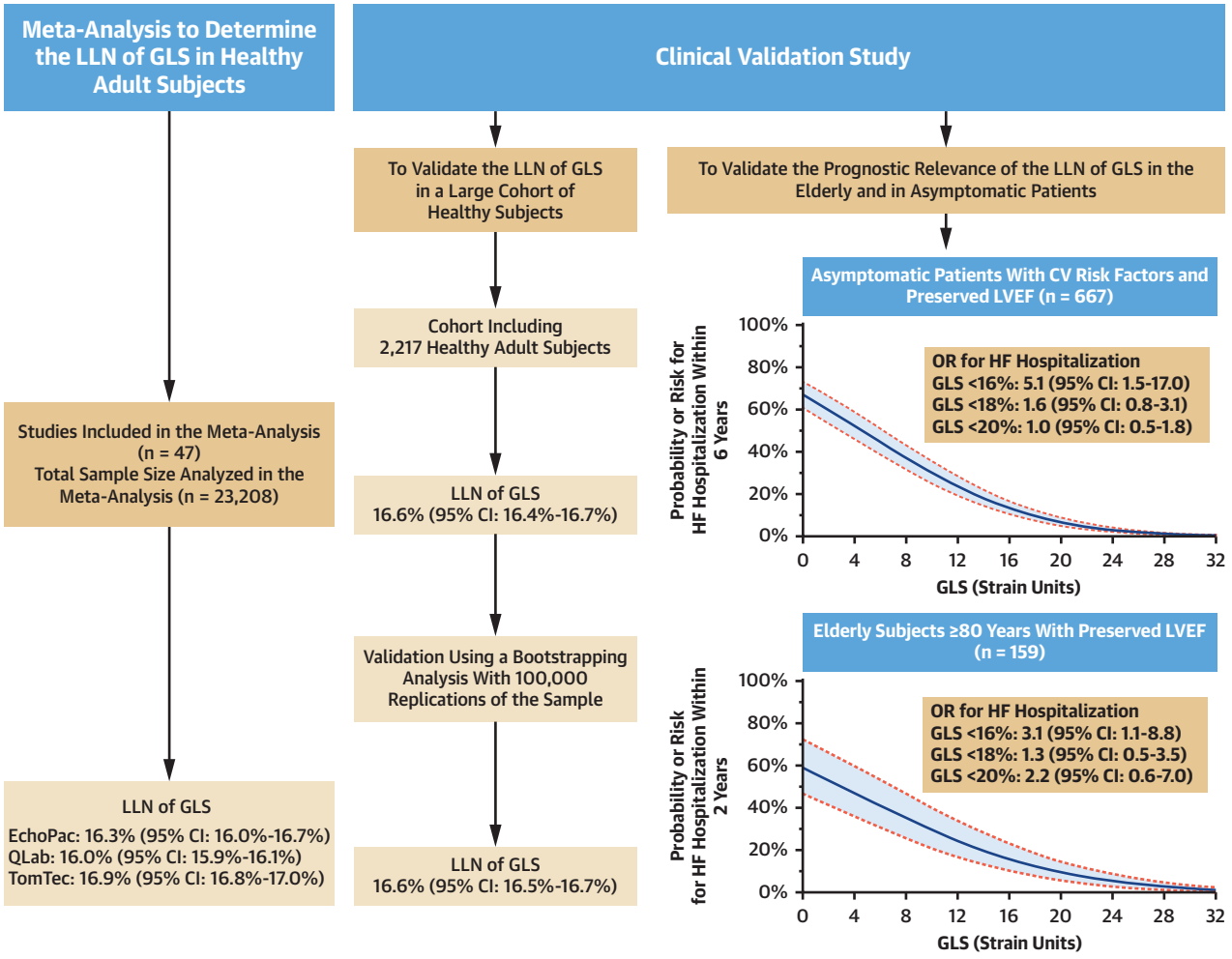
CENTRAL ILLUSTRATION **LLN of GLS and Its Prognostic Relevance in Asymptomatic Patients With Preserved LVEF at Risk for HF and in the Elderly**



Morris DA, et al. JACC Cardiovasc Imaging. 2025;18(5):525–536.

This clinical validation study, which first performed a meta-analysis including 23,208 healthy adult subjects and then conducted a large validation study including 2,217 healthy subjects, 667 asymptomatic patients, and 159 elderly subjects ≥80 years of age, provides important clinical data concerning the LLN of GLS (identified and validated at 16%) and its prognostic relevance in asymptomatic patients with preserved LVEF at risk for HF and in the elderly. GLS = global longitudinal strain; HF = heart failure; LLN = lower limit of the reference normal range; LVEF = left ventricular ejection fraction.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: This clinical validation study provides important data for cardiologists and general practitioners to determine a normal or abnormal value of GLS in daily clinical practice.

TRANSLATIONAL OUTLOOK: Knowing the specific cutoff of GLS that accurately defines an abnormal value and determines the risk for adverse CV outcomes will be of pivotal importance for the management of patients and elderly individuals with CV risk factors and preserved LVEF, such as those with arterial hypertension, to accurately determine target organ damage. In addition, these findings will help identify patients at higher risk for HF and thereby improve patient outcomes with preventive interventions.

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KEY WORDS **echocardiography, GLS, healthy, heart failure, speckle tracking, strain**

APPENDIX **For an expanded Methods section as well as supplemental figures, tables, and references, please see the online version of this paper.**