Diagnostic and Prognostic Value of Several Color Doppler Jet Grading Methods in Patients With Mitral Regurgitation

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Color Doppler is a widely used ultrasound imaging method for assessing mitral regurgitation (MR) in clinical practice. Nevertheless, color Doppler-based grading of the MR jet has been rarely considered in clinical studies. We investigated the diagnostic and prognostic value of several color Doppler MR jet grading methods and compared them with quantitative grading of MR. The MR color Doppler jet was assessed in 476 MR patients using an 'integrated' eyeballing approach by quantifying the color Doppler jet area, jet area/left atrium area and jet length and using quantitative methods. Clinical endpoints were scored as major adverse clinical events, including cardiovascular death, heart failure hospitalization and mitral valve intervention. When assessed by three echocardiographers, there was a moderate inter-observer agreement for eyeballing color Doppler grade of MR (intraclass correlation coefficient 0.69, $p < 0.001$). The intra-observer agreement was good for all color Doppler approaches. In primary MR, eyeballing color Doppler correlated well with (in)direct measures of MR severity, with a negative predictive value of 91% when using a grade 2 color Doppler as cut-off. In secondary MR, eyeballing color Doppler grade and jet length were predictors of clinical outcome in Cox proportional hazards analysis ($p = 0.003$), independent of pulmonary pressures, atrial and ventricular volumes. Overall, the integrated eyeballing approach performed better than color Doppler quantification of the MR jet area and length. In conclusion, this study shows that color Doppler grading of the distal MR jet performs well in predicting events in primary and secondary MR, compared to quantitative grading methods. **(Am J Cardiol 2021;143:111−117)**

Color Doppler-based grading of mitral regurgitation (MR) has mainly focused on assessing the flow convergence zone and the vena contracta, whereas quantification of the downstream MR jet in the left atrium (LA) has been progressively abandoned because several physical issues and echo machine settings were shown to blur the relation between the true regurgitant blood volume and the color Doppler-measured area of the MR jet in the LA.[1] Therefore, guidelines on MR recommend "qualitative" color Doppler only for assessing the presence of MR, followed by a quantitative echocardiographic method. Yet, it was shown in real world clinical practice that up to 90% of echocardiographers use color Doppler MR jet assessment for MR grading, whereas quantitative methods were used in less than half of patients.[2] In this study, we prospectively investigated the prognostic value of grading the color Doppler MR jet in primary (PMR) and secondary MR (SMR). We additionally performed a comparative analysis with (semi-)quantitative grading methods such as the vena contracta width (VCW), proximal isovelocity surface area (PISA)-based methods and the average pixel intensity (API) method, a MR grading method based on the pixel intensity of the MR continuous wave Doppler envelope.[3,4]

Methods

Transthoracic echocardiography was performed prospectively at Ghent University Hospital in 476 patients with MR of different etiologies, of whom 254 patients with PMR (136 with mitral valve prolapse and 118 with nonprolapse degenerative MR) and 223 heart failure patients with ejection fraction <50% and SMR. The study was approved by the local Ethics Committee.

We performed an online survey among 50 Belgian cardiologists on the use of all possible echocardiographic approaches for grading MR.

The VIVID9 XDclear echocardiography system with M5Sc-D probe (General Electric, Waukesha, WI) was used for all patients. All machine settings were fixed for all patients to exclude variability due to machine settings.[4]

Color Doppler assessment of MR was performed using four different approaches (Figure 1): (A) Qualitative color Doppler grading of the MR jet was performed using a *"best educated guess" (BEG) strategy*, which refers to a 'eyeballing approach of the color Doppler jet that visually integrates timing of MR, jet extent, jet orientation, relative LA area and chamber geometry.[5,6] This is also important for assessing eccentric jets that are considered to be smaller than free, central jets for the same regurgitant flow.[5,7] This

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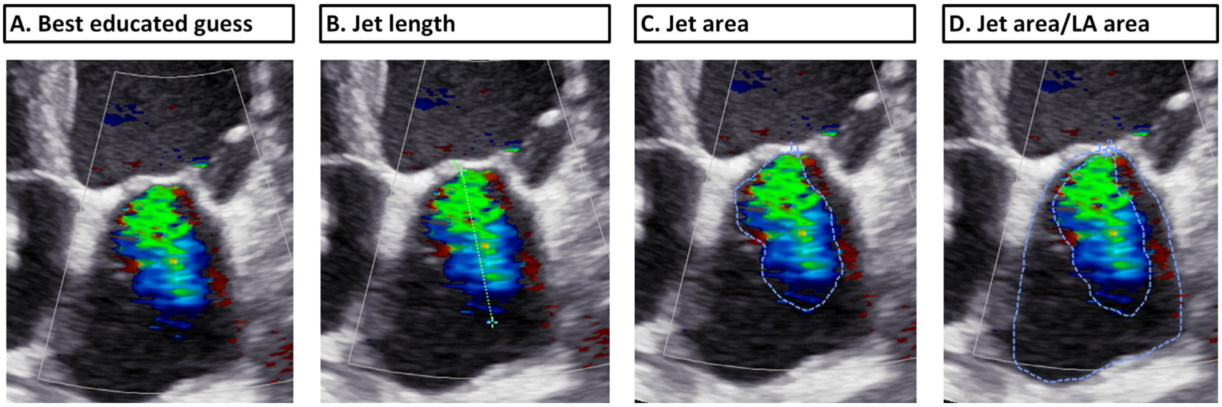

Figure 1. Different color Doppler grading approaches
The mitral regurgitation (MR) severity is assessed by color Doppler using four different approaches: (*A*) a 'best educated guess' strategy, which is an eyeballing approach of the color Doppler jet (grade 1-4) that visually 'integrates' timing of MR, jet extent, jet orientation, relative let atrial (LA) area and chamber geometry; (*B*) maximal jet length (cm); (*C*) maximal jet area (cm^2); and (*D*) the ratio of jet area/LA area (%).

BEG approach was performed by an experienced operator who graded the MR jet as grade 1, 2, 3, or 4, taking into account the aforementioned jet dynamics and characteristics. A grade 1 color Doppler jet is considered when a small jet is observed in the LA; grade 2 MR extends deeper into the LA without reaching the LA roof; grade 3 involves jets reaching the LA roof, being either central or eccentric jets; grade 4 is an MR jet (almost) filling the entire LA (see Figure 2 for representative examples).

(B) Measurement of the color Doppler MR jet length in the LA (in cm). For these measurements, the frame with the largest jet length was considered.

(C) The color Doppler MR jet was also quantitatively assessed, by measuring the color MR jet area (in cm^2) in the parasternal long axis (PLAX) and apical 4 chamber (AP4CH) view.

(D) The ratio of the AP4CH color MR jet area and/or LA area (in %)

For the inter-observer study, two other echocardiographers were instructed on these approaches. For (semi-) quantitative MR grading, VCW and PISA-based methods were assessed according to guidelines recommendations.[1,8] The API method was applied with fixed machine settings and analyzed off-line using custom-made software, as previously described.[4] All echocardiographic acquisitions, including color Doppler grading, were made by an experienced operator.

Clinical outcome was assessed using patient records. Major adverse cardiac events (MACE) were prespecified and included cardiovascular mortality, hospitalization for decompensated HF, mitral valve surgery or percutaneous intervention. Decisions for mitral valve intervention were made by an independent multi-disciplinary team based on the patient's symptoms and an integrated assessment of MR severity.

Continuous variables are expressed as mean ± SD (or median with interquartile range for non-normal distributions) and dichotomous variables as percentage. Normality of data distribution was tested with Shapiro-Wilk test. Inter- and intra- observer agreement was tested with intra-class correlation coefficient and Cohen's kappa. Correlations were calculated using Pearson's or Spearman's correlation coefficient. For survival analysis, Cox proportional hazard model was used to calculate hazard ratio. Values <0.05

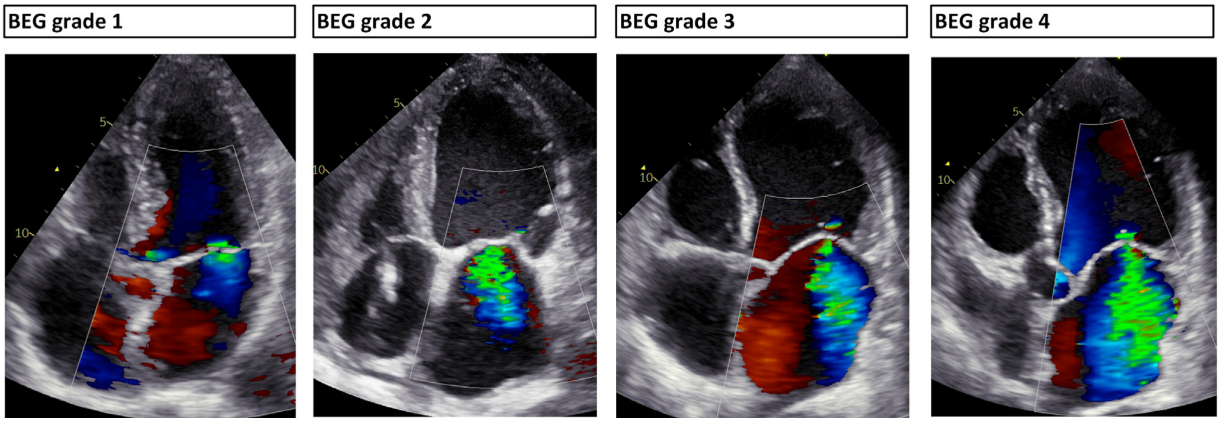

Figure 2. Examples of the best educated guess (BEG) color Doppler grading
A grade 1 color Doppler jet is considered when a small single jet is observed in the left atrium (LA); grade 2 mitral regurgitation (MR) extends deeper into the LA without reaching the LA roof; grade 3 involves jets reaching the LA roof, being either central or eccentric jets; grade 4 is an MR jet (almost) filling the entire LA. (BEG: best educated guess)

were considered statistically significant. All statistical analyses were performed in SPSS Statistics V.22 (IBM, Armonk, NY), including plotting of receiver operator curves (ROC) and Kaplan-Meier graphs.

Results

The results from the online survey on echocardiographic MR grading show that all cardiologists (100%, n = 50) used "eyeballing" for color Doppler assessment of the MR jet (BEG), whereas only 14% performed additional MR jet area measurement. Notably, 86% of the cardiologists assessed the severity of MR with any color Doppler method, which was much more frequent than the VCW (applied by 36% of cardiologists), PISA-based methods (34%) and quantitative Doppler (8%).

Three echocardiographers with different levels of expertise (highly experienced, intermediate level and cardiologist in training) graded 100 consecutive patients with PMR (n = 48) or SMR (n = 52) using the different color Doppler approaches. Overall, there was a modest agreement (ICC 0.69; Cohen's kappa 0.31 to 0.40; all $p < 0.001$) for the BEG approach. In terms of absolute agreement, only in about half of the cases, the BEG grading was concordant between the echocardiographers. This discordance persisted among all grades of MR severity (data not shown). The inter-observer agreement for jet area tracing (ICC 0.62; kappa 0.49, $p < 0.001$) and jet length (ICC 0.78; kappa 0.42, $p < 0.001$) was slightly better. The intra-observer variability was better for the BEG approach (ICC 0.80; kappa 0.55, $p < 0.001$), jet area (ICC 0.73, kappa 0.51, $p < 0.001$) and jet length (ICC 0.85; kappa 0.61, $p < 0.001$).

The BEG grading (1 to 4) approach had considerable overlap with color Doppler jet area grading parameters (see Figure 3, *panel A*), and moderate (though significant) correlations were found with color jet area, color jet length and color jet area/LA area (R = 0.66, 0.69, and 0.50, respectively, all $p < 0.001$). The scatter plot between color jet area and jet length showed good correlations ($r = 0.74$, $p < 0.001$) (Figure 3, *panel B*) and this correlation decreased in eccentric jets and nonholosystolic jets ($r = 0.67$, $p < 0.001$). Of note, the color jet area in PLAX vs. the AP4CH showed substantial scatter (Figure 3, *panel C*), with systematically larger color jet areas in AP4CH ($r = 0.68$, $p < 0.001$).

Patient characteristics in PMR and SMR are shown in Table 1. Across all types and severities of MR, the color Doppler BEG-approach had the best correlations with the API method (R = 0.76), compared to VCW (R = 0.67), PISA-effective regurgitant orifice area (EROA) (R = 0.71) and PISA-RV (R = 0.70) ($p < 0.05$). Of all color Doppler parameters, the BEG color Doppler method had the best correlations with the quantitative parameters in the total cohort. With regard to indirect measures of MR severity (pulmonary pressures, left atrial and ventricular volumes), color Doppler BEG grade had weak correlations with LV end-diastolic volume index (R = 0.30), ejection fraction (R = -0.146), right ventricular systolic pressure (R = 0.403) and LA volume (R = 0.493) (all $p < 0.05$). Of note, jet area had significantly better correlations with direct parameters of PMR severity (PISA-EROA and PISA-RV) in central jets, compared to eccentric jets ($p < 0.001$).

In the PMR cohort (n = 254), 54 patients (23%) experienced at least one MACE: mitral valve surgery (n = 45, 18%), percutaneous mitral intervention (n = 2, 1%), cardiovascular mortality (n = 9, 4%), heart failure hospitalization (n = 5, 2%). Kaplan-Meier graphs are shown in Figure 4 *panel A* (log-rank test $p < 0.001$). A grade 1 MR on color Doppler (BEG) had a very high sensitivity (0.99), whereas grade 4 MR on color Doppler had a very high specificity (0.98) for prediction of MACE. Thus, a grade 1 and 4 severity grade on color Doppler (BEG) accurately rules out or confirms severe PMR, respectively, without need for further quantification. When considering a grade 2 cut-off, the sensitivity (0.91) remained high (sensitivity 0.20), whereas a grade 3 cut-off had both a moderate sensitivity (0.38) and specificity (0.60). In this cohort with intermediate color Doppler severity grading (BEG grade 2 and 3), we assessed the predictive value of (semi-) quantitative methods (see ROC curves in Supplemental Figure 1). Based on the Youden Index, the optimal severity cut-offs in these pooled subgroups were 112 au for the API method (sens 0.69, spec 0.77), 0.18 mm^2 for PISA-EROA (sens 0.64, spec 0.72), 34 ml for PISA-RV (sens 0.64, spec 0.72) and 5.1 mm for VCW (sens 0.69, spec 0.71). These findings point to the need for additional quantification of MR in the intermediate group scored by the BEG color Doppler grading approach.

With regard to color Doppler jet area, color Doppler jet area and/or LA area and jet length (expressed as continuous variables), ROC curves were constructed (Figure 4 *panel B, C, and D*) with areas under the curve (AUC) for color

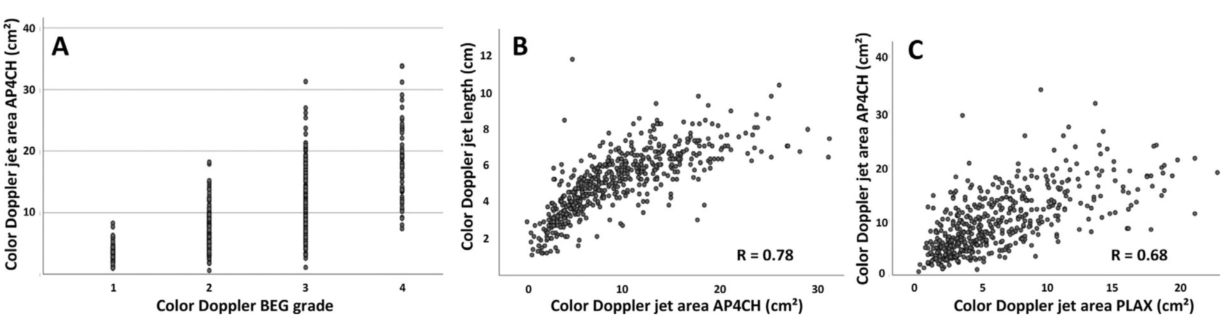

Figure 3. Comparison between different color Doppler grading methods
Panel A depicts the relationship between color Doppler grade (best educated guess (BEG)) and color Doppler jet area (AP4CH). *Panel B and C* show the relationship between the color Doppler jet area in the apical 4-chamber view (AP4CH) with either color Doppler jet length (*B*) and color Doppler jet area (*C*) in the parasternal long axis (PLAX) view.

Table 1
Clinical characteristics

	Primary MR(N=254)	Secondary MR (EF<50%)(N=223)
Age (years)	67±16	68±14
Body Mass Index (kg/m^2)	25±4	26±9
Systolic Blood Pressure (mm Hg)	142±24	129±13
Diastolic Blood Pressure (mm Hg)	74±15	79±15
Diabetes Mellitus	12%	21%
Ischemic heart disease	1%	44%
Left Atrium volume index (ml/m^2)	45±25	56±20
Left Ventricle EDD index (mm/m^2)	27±4	32±5
Left Ventricle ESD index (mm/m^2)	18±4	27±6
Left Ventricle EDV index (ml/m^2)	54 [13]	81 [41]
Left Ventricle ESV index (ml/m^2)	24 [11]	51 [34]
Ejection Fraction (%)	58 [9]	36 [15]
Right Ventrical Systolic Pressure (mm Hg)	34 [17]	44 (15)
NYHA class	1.42 (0.6)	1.9 (0.8)
Color Doppler grade 1	15%	7%
Color Doppler grade 2	33%	31%
Color Doppler grade 3	41%	48%
Color Doppler grade 4	11%	14%
Color area PLAX (cm^2)	5.1 (3.9)	8.2 (5.3)
Color area AP4CH (cm^2)	8.5 (5.7)	11.6 (5.2)
Color Doppler jet length	4.7 (1.6)	5.6 (2.3)
Color Doppler area/LA area (%)	39 [23]	49 [30]
Average Pixel Intensity (au)	94±36	118±40
PISA-EROA (cm^2)	0.14 [0.15]	0.16 (0.11)
PISA-RV (ml)	26 (32)	27 [17]
Vena Contracta Width (mm)	6.3 [2]	5.1 [2.2]

AP4CH = apical four chamber view; EDD = end-diastolic diameter; EDV = end-diastolic volume; EROA = effective regurgitant orifice area; ESD = end-systolic diameter; ESV = end-systolic volume; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; NYHA = New York Heart Association class; PISA = proximal isovelocity surface area; PLAX = parasternal long axis view; RV = regurgitant volume.

Doppler jet area (0.85), color Doppler jet area and/or LA area (0.72) and color Doppler jet length (0.82), which is comparable to API (0.84), PISA-EROA (0.83), PISA-RV (0.82) and VCW (0.84). When only considering eccentric jets, slightly higher AUC were found for the (semi-) quantitative methods (Supplemental Table 1).

Based on Youden Index, for holosystolic MR jets the optimal cut-off values for color Doppler jet area, color Doppler jet area/LA area and color Doppler jet length were 10.5 cm^2 (sens 0.70 and spec 0.85), 44% (sens 0.62, spec 0.70) and 5.5 cm (sens 0.68 and spec 0.80), respectively. In the cohort with non-holosystolic MR jets, too few events occurred for analysis which reflects their more benign course.[4,9]

In the cohort with SMR, (n = 223), MACE occurred in 99 patients (43%): surgical or percutaneous mitral valve intervention (n = 22, 10%), cardiovascular mortality (n = 50, 22%), HF hospitalization (n = 46, 21%), heart transplantation (n = 5, 2%)). Median follow-up time was 24 months. Figure 5, *panel A* shows the Kaplan-Meier graphs for BEG color Doppler grading. Similar to PMR, in SMR BEG grade 1 has a very high sensitivity (0.97) and grade 4 has a very high specificity (0.98). In the intermediate range, the odds ratio for grade 3 compared to grade 2 color Doppler was 3.16 (1.59 to 6.27; p <0.001). The optimal severity cut-offs for the (semi-)quantitative methods in the pooled BEG grades 2 and 3 were 105 au for the API

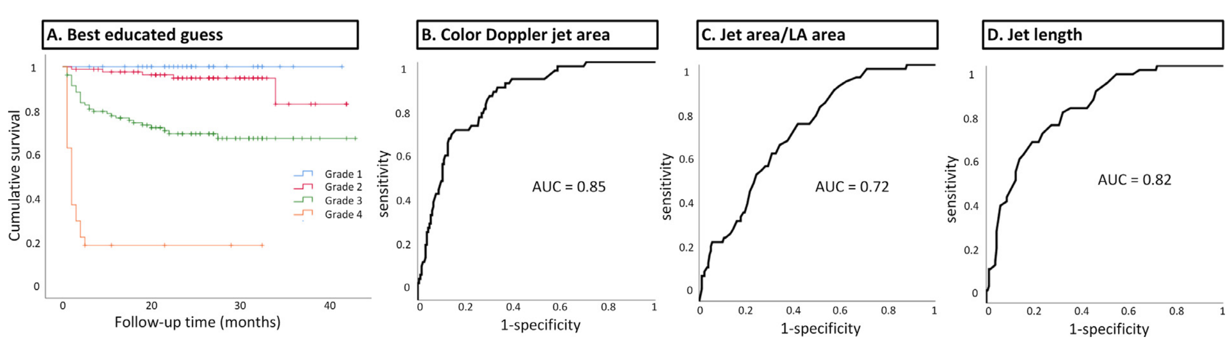

Figure 4. Survival curves in primary MR. Kaplan-Meier analysis per grade using the best educated guess method (*panel A*) and receiver operating curve (ROC) analysis for color Doppler area, color Doppler jet area/left atrium area and jet length (*panel B, C, and D*) in primary mitral regurgitation.

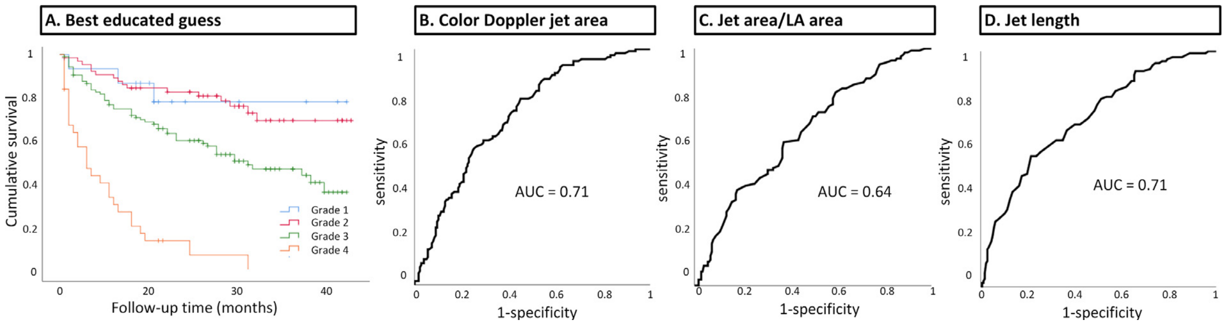

Figure 5. survival curves in secondary MR. Kaplan-Meier analysis per grade using the best educated guess method (*panel A*) and ROC curve analysis for color Doppler area, color Doppler jet area/left atrium area and jet length (*panel B, C, and D*) in primary mitral regurgitation.

method (sens 0.69, spec 0.54), 0.13 mm^2 for PISA-EROA (sens 0.60, spec 0.52), 26 ml for PISA-RV (sens 0.59, spec 0.60) and 5.1 mm for VCW (sens 0.69, spec 0.71) (Supplemental Figure 2).

The AUC for the ROC curves (see Figure 5, *panel B, C, and D* and Supplemental Table 1) for color Doppler jet area, color Doppler jet area and/or LA area and color Doppler jet length were 0.71, 0.64 and 0.71, respectively, which is comparable to API (0.72), PISA-EROA (0.72), PISA-RV (0.70) and VCW (0.69). In eccentric jets, AUC were generally higher compared to central jets (e.g. PISA-EROA 0.84 vs 0.69; p <0.001) (Supplemental Table 1).

On Cox proportional hazard analysis, using a model with all relevant echocardiographic and hemodynamic variables (Table 2), color Doppler was an independent predictor of clinical outcome when assessed by BEG MR grade and MR jet length but not when using color Doppler jet area or color Doppler jet area and/or LA area. Among the quantitative grading parameters, only the API method was an independent predictor of clinical outcome, whereas PISA-EROA and PISA-RV were not in this Cox model.[4] For eccentric SMR jets, the BEG grading approach was not a significant predictor in this model, nor were color jet length, color Doppler jet area (p = 0.35) or color Doppler jet area and/or LA area.

Discussion

The present study is the first comprehensive comparative analysis of various color Doppler methods and quantitative grading methods in predicting outcome in both PMR and SMR.

Our online survey showed that among cardiologists, color Doppler grading of the MR jet in the LA appears to be the most applied method for grading MR severity in clinical practice. This is in line with the study from Wang et al. who showed that up to 90% of echocardiographers use color Doppler jet assessment for MR grading, whereas quantitative methods are used in less than half of the patients.[2] This important gap between real world clinical practice and guideline-recommended MR grading may be attributed to the difficulties reported on quantitative MR grading methods.[1] In contrast, ‘eyeballing’ assessment of the MR color Doppler jet is a simple, fast and straightforward approach. Issues on color Doppler grading of MR may relate to its reproducibility and the impact of machine settings on the extent of the color Doppler MR jet. In addition, physical or hydrodynamic factors (jet eccentricity, atrial pressure) were shown to complicate the relationship between the true MR jet volume and the extent of the color Doppler MR jet.[1] Finally, the displayed color Doppler jet reflects a velocity map at a given time frame, and not the absolute regurgitant volume.[10] Despite these limitations, it is recognized that color Doppler assessment of the MR jet operates well at the extremes of the MR spectrum (MR grade 1 and grade 4),[1] whereas color Doppler grade 2 and 3 require additional quantification.[8]

Previously, the value of color Doppler-based MR grading was assessed by several groups.[6,11,12] However, very few clinical outcome studies considered color Doppler MR jet imaging as a grading tool. In PMR, color Doppler jet area was shown to be a predictor of outcome in univariate analysis, but not on multivariate analysis.[12] For SMR, Cioffi[13] and Koelling[14] demonstrated that color Doppler grading of the MR jet in the LA independently predicts outcome in SMR, but no comparison with quantitative methods was performed in these studies. More recently, integrative MR grading approaches have been proposed,[11,15] but these reports did not investigate or specify the value of color Doppler MR grading.

In the present study, a “BEG” color Doppler MR grading approach was adopted, which visually ‘integrates’ multiple features of the MR jet that have been linked to severe or non-severe MR.[5,6] Our results show that this BEG approach, when performed by an experienced operator, is highly feasible and predictive for clinical outcome in both PMR and SMR. Also, quantification of the MR jet area and jet length may have a similar or even better predictive performance compared to other grading parameters such as the API method, PISA-EROA, PISA-RV and VCW. These data may seem provocative or contra-intuitive, yet our results align with previous studies using a similar color Doppler grading approach.[6] The comparable predictive value of quantitative methods versus color Doppler grading in MR probably reflects a trade-off between the specific pros and cons of each method: for instance, the PISA-method as a robust theoretical hydrodynamic concept being crumbled by its limitations encountered in vivo (e.g., flow convergence zone (FCZ) flattening).[1,16] For the quantitative methods, higher overall AUCs were observed for eccentric jets, and especially the PISA method performed relatively well in eccentric SMR. The reasons for the latter are speculative, but it could reflect less flattening of the FCZ in eccentric SMR due to altered orifice geometry and leaflet angle.

Table 2
Cox proportional hazards analysis

	Cox proportional hazard analysis		
	RR	95% CI	p-value
Age	1.001	0.985-1.018	0.899
LA vol/BSA	1.003	0.993-1.013	0.574
CMP-I	0.715	0.472-1.092	0.120
Diabetes Mellitus	0.74	0.450-1.242	0.261
Atrial Fibrillation	1.059	0.668-1.796	0.45
LVEDV	1.002	0.999-1.005	0.247
NYHA class (per class step-up)	**1.63**	1.274-2.087	**<0.001**
RVSP (per 10 mmHg increase)	**1.41**	1.184-1.674	**<0.001**
Ejection Fraction (per 10% decrease)	0.876	0.674-1.186	0.392
Color Doppler grade (per grade step-up)*	**2.12**	1.484-3.033	**<0.001**
Color Doppler jet area (per cm^2 step-up)*	1.029	0.977-1.068	0.197
Color Doppler jet length (per cm step-up)*	**1.32**	1.110-1.572	**0.002**
Color Doppler jet area/LA area (per % step-up)*	1.007	0.996-1.018	0.24
API (per 10 au increase)*	**1.090**	1.030-1.116	**0.003**
PISA-EROA (per 10 mm^2 increase)*	1.14	0.874-1.405	0.18
PISA-RV (per 10 ml increase)*	1.10	0.936-1.401	0.27
VCW (per 1 mm increase)*	**1.27**	1.048-1.539	**0.015**

Bold values indicate statistically significant results.
AF = atrial fibrillation; BSA = body surface area; CMP-I = ischemic cardiomyopathy.
* Either color Doppler grade, color Doppler jet area, color Doppler jet length, color Doppler jet area/LA area, API, PISA-EROA, PISA-RV or VCW replaces API in this multivariate Cox model as MR grading parameter; no significant changes in RR occur for the other variables in this model, compared to the model above including color Doppler BEG.

As with any MR grading method, and apart from technical issues or machine settings, color Doppler grading clearly has its limitations. First, interobserver agreement for color Doppler-based approaches were moderate in our study but a similar interobserver agreement was previously shown, and comparable with the VCW and PISA-based quantitative grading methods.[17] On the other hand, the inter-observer data showed good agreements for all color Doppler approaches. Second, numerical grading remains important for serial follow-up of patients with MR. Quantification of jet area or jet length may therefore be better suited than the BEG approach, however they are not predictive in case of eccentric jets in SMR. This is one of the reasons why quantitation of EROA or RV remains essential for the multiparametric assessment of MR.[4] Finally, no standardization exists for the BEG approach, which restricts its implementation into guidelines and research settings.

Among the quantitative grading parameters, the API method had the best correlations with indirect parameters of MR severity in PMR, and API was the only independent predictor of outcome on multivariable Cox regression analysis in SMR.[18] API grades MR severity based on the pixel intensity of the CW Doppler envelope and shares several advantages compared to other grading methods: it is highly feasible in several types of MR, it has a fast and easy application and integrates multiple components and determinants of MR severity.[4] Furthermore, the API method is complementary to color Doppler jet grading, as (1) it has a higher inter-observer agreement,[3] (2) it readily reveals non-holosystolic jets,[19] and (3) it inherently provides a larger range of MR severities. Therefore a multi-parametric grading of MR remains the reference approach in clinical practice for diagnosis, risk stratification and therapeutic decision-making.

The current study has limitations. Color Doppler was assessed in AP4CH and PLAX view, but not in the AP2CH view. We excluded patients with multiple jets, although this cohort comprised a small number of patients with multiple jets.[4,18] In the current study, we had no inter- and intra-observer data for the quantitative grading methods to compare with the color Doppler-based grading approaches. Comparison of color Doppler with CMR as another reference method was not performed. In the PMR cohort, Cox proportional hazards analysis was not performed, because too many events occurred early in the follow-up and of because the limited patient number.

In conclusion, we showed that grading MR with color Doppler is most frequently used in clinical practice and predicts outcome in PMR and SMR, comparable to established quantitative methods. A multiparametric assessment remains the reference approach for grading MR.

Authors' Contributions

Victor Kamoen: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Visualization; Simon Calle: Investigation, Writing - Review & Editing; Milad El Haddad: Software, Resources; Tine De Backer: Validation, Writing - Review & Editing; Marc De Buyzere: Validation, Writing - Review & Editing; Frank Timmermans: Conceptualization, Methodology, Investigation, Writing - Original Draft

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.027.

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