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# Vessel-Oriented Analysis on the Relationship Between Quantitative-Flow Ratio and Mortality in Patients With Severe Aortic Stenosis and Intermediate Coronary Lesions

Iginio Colaiori[1] | Luca Paolucci[2] | Fabio Mangiacapra[3] | Emanuele Barbato[4] | Giulia Nardi[2] | Javier Escaned[2] | Gianluca Campo[5] | Simone Biscaglia[5] | Francesco Versaci[1] | Giuseppe Biondi-Zoccai[6,7] | Achille Gaspardone[8] | Marco Vitolo[9] | Giorgio Benatti[10] | Luigi Vignali[10] | Giuseppe Boriani[9] | Vincenzo Guiducci[11]

[1]Division of Cardiology, Santa Maria Goretti Hospital, Latina, Italy | [2]Department of Cardiology, Hospital Clinico San Carlos, Madrid, Spain | [3]Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy | [4]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy | [5]Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy | [6]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy | [7]Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy | [8]Division of Cardiology, Sant' Eugenio Hospital, Rome, Italy | [9]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy | [10]Cardiology Department, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy | [11]Cardiology Unit, Azienda USL-IRCCS Reggio Emilia, S. Maria Nuova Hospital, Reggio Emilia, Italy

**Correspondence:** Fabio Mangiacapra (f.mangiacapra@policlinicocampus.it)

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## ABSTRACT

**Background:** Quantitative flow ratio (QFR) is effective in predicting mortality in patients undergoing transcatheter aortic valve replacement (TAVR). How QFR reclassifies coronary artery disease (CAD) at vessel-level compared to angiography and how this influences the risk of death, remains undetermined.

**Methods:** We calculated QFR from consecutive 280 TAVR patients with bystander coronary stenoses. All lesions were managed conservatively. Angiographic CAD was defined by a diameter stenosis ≥ 50%, functional CAD by a QFR ≤ 0.80. The outcome was mortality at 3 years.

**Results:** Overall, 635 lesions were included. Angiographic CAD was evident in 165 (26.0%), functional CAD in 17 (11.2%) (reclassification: $p < 0.001$). Angiography/QFR mismatch occurred in 22.5%, mostly in large vessels and lesions located in the proximal left anterior descending (LAD). QFR ≤ 0.80 was an independent predictor of death (HR 2.91, 95% CI 1.94−4.36; $p < 0.001$). The risk was progressively increased for lower QFR values and positive QFR at LAD site (vs. QFR > 0.80 HR: 3.92, 95% CI 2.78−5.53; $p < 0.001$; vs. QFR ≤ 0.80 at non-LAD site: HR 2.65, 95% CI 1.07−6.59; $p = 0.034$).

**Conclusions:** QFR leads to a significant reclassification of CAD rates at vessel-level and shows a significant prognostic value in patients undergoing TAVR.

Iginio Colaiori and Luca Paolucci have equally contributed to this work.

## 1 | Introduction

Transcatheter aortic valve replacement (TAVR) has gained a progressively major role in the management of aortic stenosis (AS), thanks to strong data supporting its efficacy and safety in patients at high- and intermediate-surgical risk [1, 2]. The prevalence of coronary artery disease (CAD) in these subjects is significant, despite different incidences having been reported [3]. Conflicting data have been previously published regarding the prognostic value of CAD [4–6] and the role of revascularization in this setting [7, 8]. Some of these heterogeneous reports may be related to the application of an angiographic parameter to estimate the severity of CAD, which doesn't account for the actual hemodynamic relevance of coronary stenoses. Recently, we demonstrated that non-invasive physiological evaluation of coronary lesions by means of quantitative flow ratio (QFR) is associated with a significantly improved prognostic stratification of these subjects [9]. However, it is still unknown how QFR can lead to a reclassification of CAD patterns and if it can depict a continuously increased risk of adverse events in this setting, similarly to what has been previously reported for fractional-flow reserve (FFR) [10]. In this study on patients undergoing TAVR and conservative management of bystander coronary stenoses, we aimed to (1) estimate how the application of QFR influences the features and patterns of CAD compared to angiography and (2) to assess the relationship between vessel-level QFR values and mortality, according to stenosis' location and hemodynamic severity.

## 2 | Methods

### 2.1 | Study Design and Population

We performed a retrospective analysis of angiographic data in patients with severe AS treated with TAVR in four Italian centers. All patients underwent coronary angiography before the TAVR procedures. The main inclusion criterion was the presence of at least one intermediate coronary lesion in one of the three main coronary arteries (left anterior descending [LAD]; left circumflex [LCx], right coronary artery [RCA]), defined by a diameter of stenosis (DS) comprised between 20% and 90%. Patients with acute coronary syndromes, aorto-ostial disease, left main disease, myocardial bridging, poor angiography image quality, absence of two angiographic projections separated by more than 25°, angiograms with frame rate < 12.5 frames per second, and severe tortuosity or overlapping limiting an optimal 3D reconstruction of the target vessel were excluded. Severe AS was defined by a valve area < 1.0 $cm^2$ (indexed valve area < 0.6 $cm^2/m^2$ body surface area) or flow-pressure parameters (mean gradient > 40 mmHg, maximum jet velocity > 4.0 m/s, and velocity ratio < 0.25). QFR analyses on vessels showing intermediate CAD were performed by certified analysts blinded to clinical data. Coronary revascularization was routinely deferred, and all patients underwent medical treatment. All the patients included signed an informed consent. The present study was conducted in accordance with the statements of the Declaration of Helsinki.

### 2.2 | QFR Estimation and Angiographic Parameters

QFR was calculated in all coronary arteries showing intermediate CAD offline with the QAngio-XA 3D software (research edition, version 1.1; Medis, Leiden, the Netherlands) after selecting two angiographic projections separated by at least 25° in the end-diastolic frames. Angiographic lesions' severity was defined by DS% after quantitative coronary angiography evaluation. For vessels showing multiple lesions, only the most severe were selected. Other parameters collected were minimal lumen diameter (MLD), reference lumen diameter (RLD), and lesion length (LL). Eventually, a fixed QFR value derived from computing 3D-QCA data with a fixed flow was modeled to patient-specific flow properties after simulating hyperemic conditions combining frame count analysis and vessel lumen volume ("contrast-QFR," in this study simply reported as "QFR"). Angiographic definition of CAD was applied to vessels showing at least one lesion with a DS ≥ 50%, while the physiological definition of CAD was applied to vessels with a QFR ≤ 0.80. The SYNTAX score (SS) was derived at the patient-level by using standard angiographic evaluation [11]. The functional SYNTAX score (FSS) was derived by applying the traditional SS criteria only to vessels with physiologically defined CAD.

### 2.3 | Study Endpoint

The main endpoint was all-cause mortality at 3 years of follow-up. Data on the outcome of interest were collected in the regional dataset of Emilia-Romagna.

### 2.4 | Statistics

All analyses were conducted at the vessel level unless reported otherwise. Categorical variables are described as rates and percentages (%), continuous variables as mean with standard deviation or median and interquartile range (IQ). Comparisons between groups were performed with Pearsons' chi square and Mann–Whitney *U* test, respectively. Normal distribution for continuous variables was tested with the Shapiro–Wilk test. Correlation between DS% and QFR was evaluated with Kendall's rank test. Discrimination analyses for positive QFR or death were conducted with receiver operator characterizing (ROC) curve and area under the curve (AUC) derivation. Comparisons between ROC curves were performed with the DeLong test. Reclassification of significant CAD between angiography and QFR was investigated with McNemar's test. Predictors of QFR ≤ 0.80 and angiography/QFR mismatch were investigated with step-forward multivariate logistic regression (entry level: $p = 0.100$) and reported as odds ratio (OR) and 95% confidence intervals (CI). The relationship between ordinal values of QFR and death was described with the Cochrane-Armitage test. The association with the outcome against the standard reference of positive and negative mismatch/concordance between angiography and QFR was investigated with univariate Cox's regression. Similar analysis was conducted in patients with or without significant LAD disease. Independent predictors of death were tested in a step-forward multivariate

Cox's regression (entry level $p = 0.100$) and their association reported as hazard ratio (HR) and 95% CI. The proportional hazard assumption was tested with Schoenfeld's residuals. All vessel-level regression analyses were clustered at the patient-level with robust standard errors. Statistical significance was set at a $p$ value $< 0.05$ (two-tails, unadjusted for multiplicity). No imputation for missing data was performed. Statistical analysis was performed using STATA 16 (Stata Corp, College Station, TX, USA) and GraphPad Prism 8 (GraphPad Software, San Diego, California, USA).

## 3 | Results

### 3.1 | Main Features and Predictors of Positive QFR

Between February 2009 and December 2019, 451 consecutive patients underwent TAVR for severe AS. Within these patients, 133 patients were excluded due to the lack of angiographic data. The other 38 patients were excluded because they did not fulfill the angiographic inclusion criteria. Overall, 280 patients with 635 intermediate coronary lesions were included in this study. The main clinical and anatomic features of the enrolled cohort are depicted in Table 1. At the patient-level, subjects with at least one QFR-positive lesion showed higher rates of previous MI (26.1% vs. 9.3%; $p < 0.001$) and previous PCI (27.7% vs. 15.3%; $p = 0.024$). Anatomic burden of CAD was generally low in the entire cohort, with an SS of 2.34 (±3.02) and an FSS of 1.46 (±2.90). When considering only patients with significant CAD, SS was 4.2 (±2.87) and FSS 6.3 (±2.39). At the vessel level, QFR-positive lesions generally showed lower MLD, greater LL, and DS% (the data are reported for each coronary artery in Table 1). The distribution of QFR values can be found in Figure S1. At multivariate vessel-level regression analysis, previous MI, proximal LAD lesion location, MLD, LL, and DS% ≥ 50% were independent predictors of positive QFR (Table 2).

### 3.2 | CAD Reclassification and Mismatch Analysis

Correlation analysis between DS% and QFR values and discrimination analysis for QFR ≤ 0.80 can be found in Figures S2 and S3. Overall, angiography-defined CAD was found in 127 (45.3%) patients, while 65 (23.2%) showed at least one QFR-positive lesion, which was associated with a significant CAD reclassification rate ($p < 0.001$). Similarly, at the vessel-level, 165 (26.0%) lesions showed a DS ≥ 50%, while 71 (11.2%) showed a QFR ≤ 0.80, which was consistent with a significant reduction in the observed rates of CAD ($p < 0.001$). These results are summarized in Figure 1A. When angiography was considered, CAD prevalence was significantly higher in the RCA (39.4%) compared to LAD (33.9%) and LCx (26.7%) ($p < 0.001$). This pattern was dramatically changed after QFR evaluation (LAD: 73.3%; LCx: 4.2%; RCA: 22.6%; $p < 0.001$). These findings are depicted in Figure 1B. Overall, angiography/QFR mismatch occurred in 143 (22.5%) vessels, of which 28 (4.1%) showed positive mismatch (QFR ≤ 0.80 and DS < 50%), and 122 (19.2%) showed negative mismatch (QFR > 0.80 and DS ≥ 50%). According to multivariate analysis, the strongest predictor of mismatch between angiography and QFR was LAD location of positive physiology (OR 4.04, 95% CI 2.17−7.51; $p < 0.010$) and RLD (OR 1.36, 95% CI 1.01−1.83; $p = 0.044$) (see Table 3).

### 3.3 | Vessel-Level Analysis on the Relationship Between QFR and Mortality

At 3 years of follow-up, a death rate of 22.8% occurred at the vessel level. The ordinal relationship between QFR and the rate of mortality is reported in Figure 2, showing an increment of death events across each progressively lower QFR strata (0.05) (Cochrane-Armitage $p < 0.001$). Overall, the outcome occurred in the 19.3% negative-QFR lesions and 50.7% positive-QFR lesions (Kaplan−Meier curves depicted in Figure 3A). At the vessel-level, QFR ≤ 0.80 was an independent predictor of death at 3 years of follow-up (HR 2.91, 95% CI 1.94−4.36; $p < 0.001$) (see Table 4). The continuous relationship between QFR and the death risk is reported in Figure 3B. When subtypes of angiography/QFR mismatches were investigated, the severity of angiographic disease showed a weak relationship with the outcome. Specifically, no significant differences were evident between positive concordance and positive mismatch groups (HR 0.70, 95% CI 0.33−1.48; $p = 0.364$) or negative mismatch and negative concordance groups (HR 0.78, 95% CI 0.41−1.47; $p = 0.450$) (Table S1). At vessel analysis, LAD QFR-positive lesions showed a stronger association with death events when compared both with QFR negative lesions (HR 3.92, 95% CI 2.78−5.53; $p < 0.001$) and non-LAD QFR-positive lesions (HR 2.65, 95% CI 1.07−6.59; $p = 0.034$). Notably, no significant difference in terms of outcomes was evident between non-LAD QFR-positive lesions and QFR-negative lesions (HR 1.45, 95% CI 0.60−3.53; $p = 0.403$) (Figure 4B).

### 3.4 | Patient-Level Analysis of Clinical Outcome

During follow-up, 62 (22.1%) patients died, of whom 28 (13.0%) were in the QFR-negative group, and 34 (52.3%) were in the QFR-positive group. At multivariate analysis, the presence of at least one lesion with a QFR ≤ 0.80 was associated with an independently increased risk of death (HR 4.88, 95% CI 2.91−8.19; $p < 0.001$) (SM Table 2). Compared to SS, FSS showed a higher discriminative ability for mortality (FSS AUC: 0.703; SS AUC: 0.531; $p < 0.001$) (Figure 5), which was reflected by a significant association with the outcome when forced in the multivariate model (HR 1.20, 95% CI 1.13−1.28; $p < 0.001$).

## 4 | Discussion

According to our findings, QFR evaluation of coronary stenoses in patients undergoing TAVR leads to a significant reclassification of CAD features, both in terms of prevalence and vessel location. The increased sensitivity of QFR for CAD severity leads to a stronger association with the mortality risk, especially in patients with hemodynamically more severe coronary obstructions and LAD disease.

To date, several different definitions of CAD have been applied in studies investigating its prognostic role in patients with AS. Specifically, different angiographic thresholds, occasionally

**TABLE 1** | Main features of the enrolled cohort.

| **Patient-level Clinical features** | **Overall (280)** | **QFR > 0.80 (215)** | **QFR ≤ 0.80 (65)[a]** | ***p* value** |
|---|---|---|---|---|
| Age (year) | 84 (80–86) | 83 (79–86) | 85 (81–86) | 0.078 |
| Male gender | 125 (44.6) | 96 (44.6%) | 29 (44.6%) | 0.996 |
| Dyslipidemia | 149 (53.2%) | 117 (54.4%) | 32 (49.2%) | 0.463 |
| Hypertension | 245 (87.5%) | 186 (86.5%) | 59 (90.7%) | 0.363 |
| Diabetes | 75 (26.8%) | 56 (26.1%) | 19 (29.2%) | 0.611 |
| Smoke | 67 (23.9%) | 54 (25.1%) | 13 (20.0%) | 0.397 |
| CKD | 102 (36.4%) | 76 (35.3%) | 26 (40.0%) | 0.495 |
| COPD | 54 (19.3%) | 42 (19.5%) | 12 (18.5%) | 0.848 |
| Previous stroke | 29 (10.3%) | 21 (9.7%) | 8 (12.3%) | 0.556 |
| Ejection fraction | 55 (46–55) | 55 (48–55) | 55 (45–60) | 0.902 |
| Previous MI | 37 (13.2%) | 20 (9.3%) | 17 (26.1%) | < 0.001 |
| Previous PCI | 51 (18.2%) | 33 (15.3%) | 18 (27.7%) | 0.024 |
| Previous CABG | 20 (7.1%) | 16 (7.4%) | 4 (6.1%) | 0.724 |
| *Coronary features* | | | | |
| *Angio-defined CAD* | 127 (45.3%) | | | |
| SVD | 94 (33.5%) | | | |
| MVD | 33 (11.8%) | | | |
| SS | 2.34 (±3.02) | | | |
| *QFR-defined CAD* | 65 (23.2%) | | | |
| SVD | 59 (21.1%) | | | |
| MVD | 6 (2.1%) | | | |
| FSS | 1.46 (±2.90) | | | |
| **Vessel-level Coronary features** | **Overall (635)** | **QFR > 0.80 (564)** | **QFR ≤ 0.80 (71)** | ***p* value** |
| *LAD* | *244 (38.4%)* | *192 (78.7%)* | *52 (21.3%)* | — |
| RLD (mm) | 2.60 (2.30–3.00) | 2.60 (2.30–3.00) | 2.74 (2.48–3.06) | 0.204 |
| MLD (mm) | 1.70 (1.40–2.00) | 1.70 (1.50–2.00) | 1.50 (1.20–1.83) | 0.001 |
| LL (mm) | 16.80 (11.30–24.72) | 15.00 (9.72–20.32) | 24.50 (16.32–40.95) | < 0.001 |
| DS (%) | 39.0 (31.0–48.0) | 37.00 (30.00–45.00) | 45.50 (39.12–60.50) | < 0.001 |
| DS ≥ 50% | 56 (22.9%) | | | |
| QFR | 0.90 (0.83–0.97) | 0.93 (0.87–0.98) | 0.78 (0.74–0.80) | < 0.001 |
| QFR ≤ 0.80 | 52 (21.3%) | | | |
| *LCx* | *200 (38.5%)* | *197 (98.5%)* | *3 (1.5%)* | — |
| RLD (mm) | 2.72 (2.40–3.00) | 2.75 (2.40–3.00) | 2.10 (1.90–2.30) | 0.035 |
| MLD (mm) | 1.74 (1.42–2.09) | 1.75 (1.50–2.10) | 0.80 (0.60–1.00) | 0.003 |
| LL (mm) | 12.75 (8.32–19.00) | 12.70 (8.25–18.95) | 24.00 (13.20–26.00) | 0.089 |
| DS (%) | 35.00 (26.32–47.90) | 35.00 (26.15–35.00) | 82.00 (80.00–82.00) | 0.003 |
| DS ≥ 50% | 44 (22.0%) | | | |
| QFR | 0.97 (0.92–0.99) | 0.97 (0.92–0.99) | 0.74 (0.60–0.74) | 0.002 |
| QFR ≤ 0.80 | 3 (1.5%) | | | |
| *RCA* | *191 (30.1%)* | *175 (91.6%)* | *16 (8.4%)* | — |
| RLD (mm) | 3.00 (2.70–3.50) | 3.00 (2.70–3.50) | 2.80 (2.50–3.00) | 0.203 |
| MLD (mm) | 1.90 (1.50–2.27) | 1.93 (1.60–2.30) | 1.15 (0.65–1.40) | < 0.001 |
| LL (mm) | 15.00 (8.90-20.00) | 15.00 (8.90–20.00) | 13.30 (9.17–27.05) | 0.604 |
| DS (%) | 40.00 (30.00–50.00) | 38.30 (27.00–50.00) | 61.80 (58.23–88.38) | < 0.001 |

(Continues)

**TABLE 1** | (Continued)

| Vessel-level Coronary features | Overall (635) | QFR > 0.80 (564) | QFR ≤ 0.80 (71) | *p* value |
|---|---|---|---|---|
| DS ≥ 50% | 65 (34.0%) | | | |
| QFR | 0.95 (0.87–0.98) | 0.95 (0.89-0.99) | 0.75 (0.60–0.80) | < 0.001 |
| QFR ≤ 0.80 | 16 (8.3%) | | | |

[a]To be interpreted as patients with at least one QFR value ≤ 0.80.

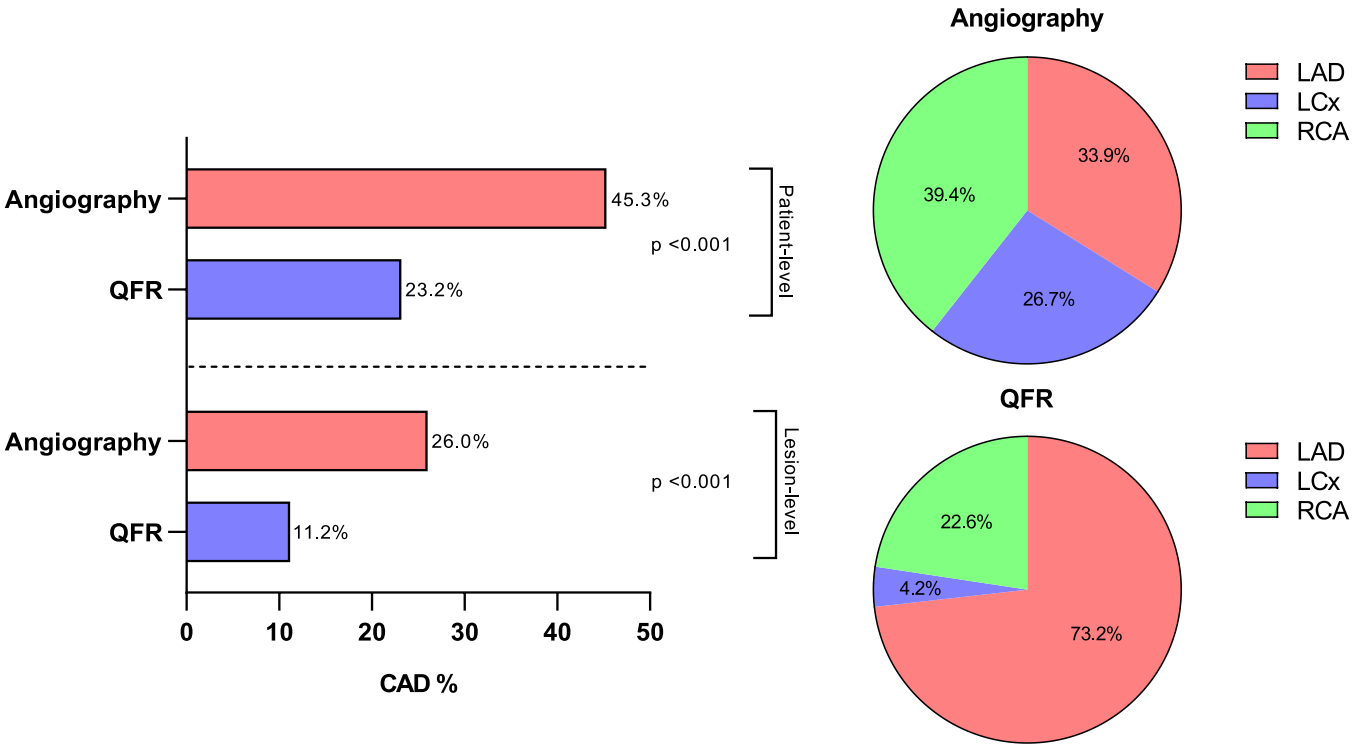


**FIGURE 1** | CAD prevalence according to angiographic and QFR evaluations. [Color figure can be viewed at wileyonlinelibrary.com]

combined with the presence of previous revascularizations or previous MI, have all been advocated as possible definitions [12–18]. Approaches that considered CAD as a bystander condition, disconnecting it from its actual hemodynamic relevance, may have contributed to the conflicting findings in terms of prognostic relevance in this setting. In our study, when QFR was applied at vessels with intermediate DS, we observed a dramatic reclassification of CAD features. First, the number of vessels (and patients) that would have been previously considered as suffering obstructive stenoses was halved. Second, the location of those obstructions was largely rearranged, shifting from a higher prevalence of DS ≥ 50% in the RCAs to a higher number of LADs showing a QFR ≤ 0.80. This may have directly influenced the association with QFR-defined CAD and mortality, as shown by the higher risk of death in subjects with hemodynamically severe stenoses of the LAD. Notably, clinical and angiographic factors as previous MI, RLD, LL, and location on the proximal LAD, were associated with a higher prevalence of QFR-positive lesions and mismatch with the angiographic stenosis degree. These findings are concordant with those coming from studies investigating the relationship between angiography and wire-based physiology [19, 20], and highlight the presence of a specific subgroup of coronary lesions that are particularly exposed to the risk of misclassification (and possibly mistreatment).

Investigations on intracoronary physiology showed that lesion-level FFR is a continuous predictor of adverse events in patients with conservatively managed CAD, with a progressively higher risk in those showing greater hemodynamic obstruction [10]. Despite the reliability of FFR in the AS setting has been questioned due to the presence of concomitant microvascular dysfunction [21, 22], recent data suggest that this may not directly influence the prognostic value of that index [23]. According to our results, a similar trend can also be evident when using non-invasive physiology. Specifically, the mortality rates after 3 years since the procedure progressively increased for lower QFR values, especially for lesions ≤ 0.75 and ≤0.70. At the patient-level, this translates in an increased discriminative capacity for the primary outcome of FSS compared to traditional SS. With the increasing implementation of coronary computed tomography (CT = in the pre-procedural planning of TAVR [24], new investigations are awaited to assess the role that non-invasive physiology may play even in that setting.

Whether this prognostic capacity could translate into guidance to direct coronary revascularization is yet to be determined.

**TABLE 2** | Independent predictors of QFR-positive lesions.

| | Uni-variate model | | Multivariate model | |
|---|---|---|---|---|
| | **OR and 95% CI** | ***p* value** | **OR and 95% CI** | ***p* value** |
| *Clinical variables* | | | | |
| Age (year) | 1.03 (0.99−1.08) | 0.125 | | |
| Male gender | 0.98 (0.60−1.61) | 0.959 | | |
| Dyslipidemia | 1.01 (0.61−1.63) | 0.979 | | |
| Hypertension | 1.48 (0.66−3.32) | 0.336 | | |
| Diabetes | 1.21 (0.71−2.08) | 0.474 | | |
| Smoke | 0.89 (0.48−1.65) | 0.722 | | |
| CKD | 1.18 (0.71−1.94) | 0.511 | | |
| COPD | 1.04 (0.55−1.96) | 0.904 | | |
| Previous stroke | 1.42 (0.67−3.02) | 0.350 | | |
| Ejection fraction | 0.99 (0.97−1.01) | 0.683 | | |
| Previous MI | 2.33 (1.35−3.97) | 0.002 | 2.49 (1.18−5.25) | 0.017 |
| Previous PCI | 1.67 (0.96−2.89) | 0.065 | 0.68 (0.32−1.46) | 0.329 |
| Previous CABG | 0.70 (0.27−1.81) | 0.468 | | |
| *Coronary variables* | | | | |
| Proximal LAD location | 4.51 (2.53−8.03) | < 0.001 | 6.84 (3.07−15.24) | < 0.001 |
| RLD (mm) | 0.80 (0.54−1.19) | 0.287 | | |
| MLD (mm) | 0.13 (0.07−0.24) | < 0.001 | 0.11 (0.05−0.27) | < 0.001 |
| LL (mm) | 1.07 (1.04−1.10) | < 0.001 | 1.08 (1.05−1.11) | < 0.001 |
| DS ≥ 50% | 5.56 (3.29−9.39) | < 0.001 | 2.79 (1.52−5.13) | 0.001 |

**TABLE 3** | Independent predictors of angiography-QFR mismatch.

| | Uni-variate model | | Multivariate model | |
|---|---|---|---|---|
| | **OR and 95% CI** | ***p* value** | **OR and 95% CI** | ***p* value** |
| *Clinical variables* | | | | |
| Age (year) | 1.02 (0.98−1.06) | 0.154 | | |
| Male gender | 0.86 (0.58−1.27) | 0.472 | | |
| Dyslipidemia | 0.93 (0.63−1.36) | 0.725 | | |
| Hypertension | 1.24 (0.68−2.26) | 0.471 | | |
| Diabetes | 1.18 (0.77−1.80) | 0.439 | | |
| Smoke | 0.84 (0.53−1.33) | 0.479 | | |
| CKD | 1.39 (0.93−2.06) | 0.100 | 1.31 (0.87−1.98) | 0.194 |
| COPD | 1.01 (0.61−1.68) | 0.297 | | |
| Previous stroke | 0.53 (0.21−1.29) | 0.164 | | |
| Ejection fraction | 1.00 (0.98−1.01) | 0.949 | | |
| Previous MI | 1.37 (0.83−2.28) | 0.213 | | |
| Previous PCI | 1.43 (0.90−2.28) | 0.124 | | |
| Previous CABG | 0.84 (0.38−1.81) | 0.658 | | |
| *Coronary variables* | | | | |
| Proximal LAD location | 1.35 (0.78−2.34) | 0.275 | | |
| Positive QFR at LAD | 4.40 (2.47−7.83) | < 0.001 | 4.04 (2.17−7.51) | < 0.001 |
| RLD (mm) | 1.31 (0.98−1.76) | 0.063 | 1.36 (1.01−1.83) | 0.044 |
| LL (mm) | 1.02 (1.00−1.04) | 0.007 | 1.00 (0.98−1.03) | 0.444 |

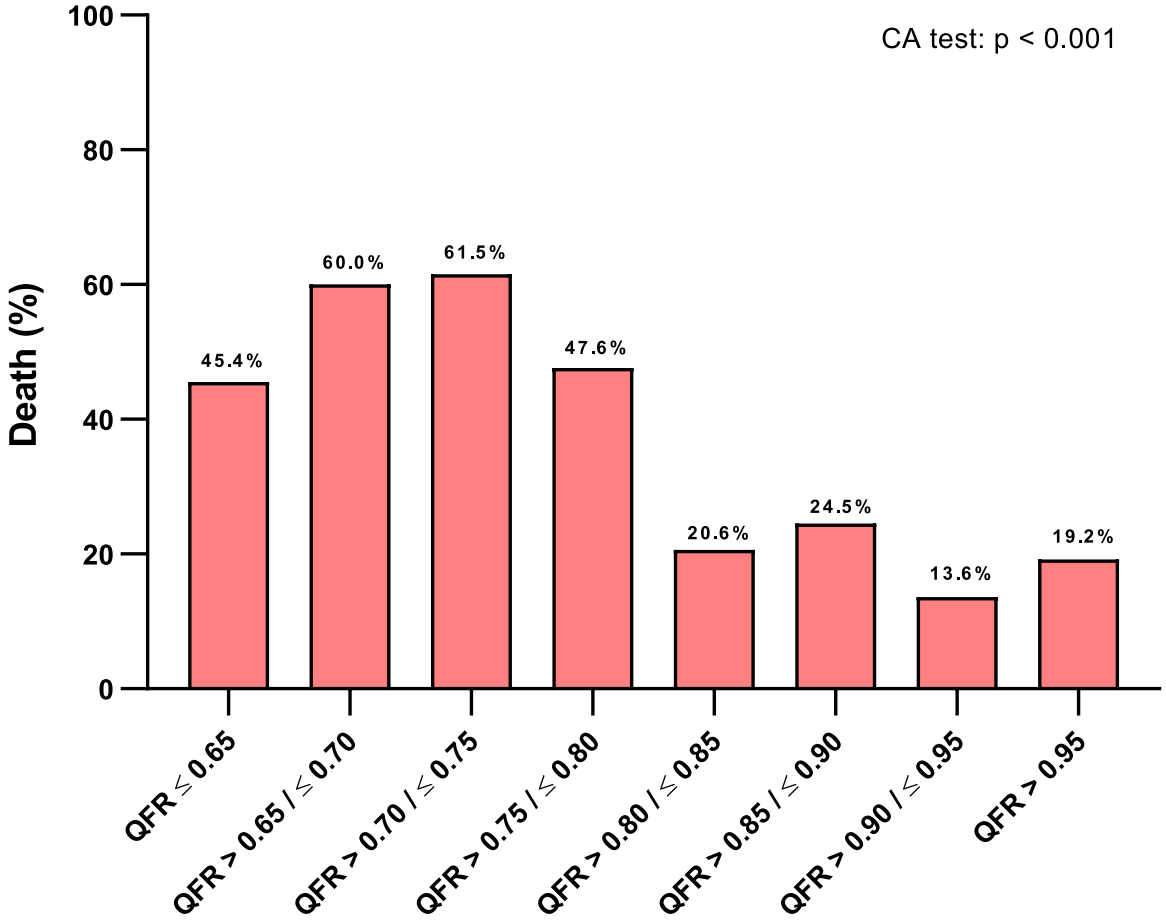


**FIGURE 2** | Ordinal relationship between QFR strata and mortality. [Color figure can be viewed at wileyonlinelibrary.com]

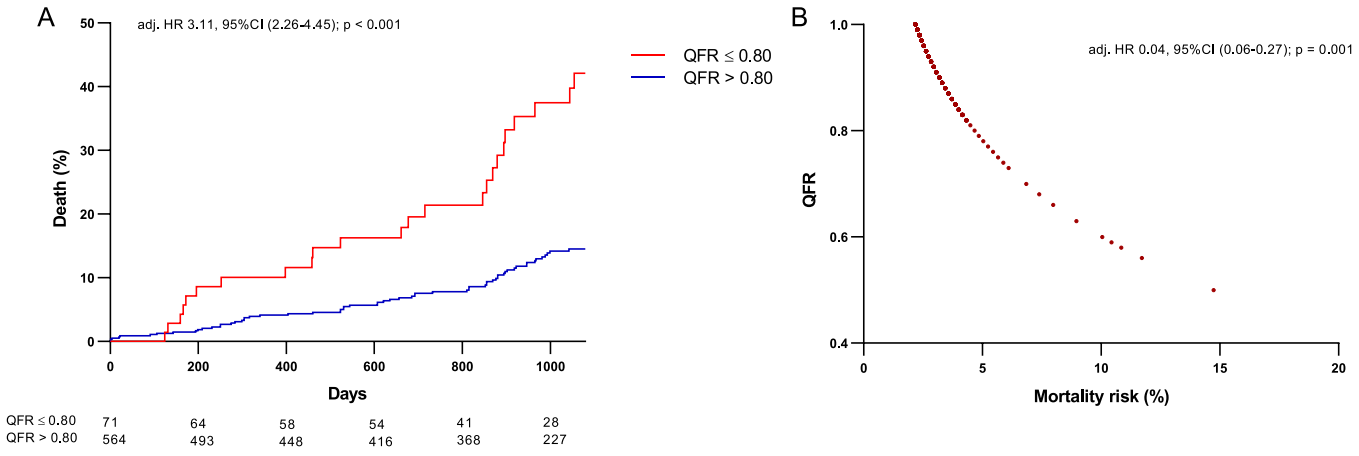


**FIGURE 3** | Discrete (A) and continuous (B) relationship between QFR and mortality. [Color figure can be viewed at wileyonlinelibrary.com]

Recently, the "Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation" (NOTION-3) trial demonstrated for the first time that an FFR-guided revascularization in patients undergoing TAVR is superior to conservative management [25]. Nevertheless, despite previous data showing a strong correlation between QFR and FFR values in these subjects [26], a cautious approach may be warranted when considering the indication for percutaneous coronary intervention. According to the data coming from the "Functional Assessment by Virtual Online Reconstruction" (FAVOR) trials in patients with stable CAD, QFR-guided revascularization is superior to angiography but inferior to FFR in terms of major clinical outcomes [27, 28]. In detail, a recent sub-analysis of the FAVOR III Europe trial has shown that the detrimental effects of QFR compared to invasive physiology may be related to an increased risk of unsafe deferrals [29]. Therefore, while the prognostic value of QFR may be hardly questionable, its safety in guiding interventions in patients with AS remains unknown. Specifically, coronary revascularization should be primarily offered to relieve angina

**TABLE 4** | Independent predictors of mortality (lesion-level).

| | Uni-variate model | | Multivariate model | |
|---|---|---|---|---|
| | **HR and 95% CI** | ***p* value** | **HR and 95% CI** | ***p* value** |
| *Clinical variables* | | | | |
| Age (year) | 1.02 (0.96–1.07) | 0.441 | | |
| Male gender | 1.52 (0.90–2.56) | 0.114 | | |
| Dyslipidemia | 0.64 (0.38–1.09) | 0.102 | | |
| Hypertension | 0.73 (0.35–1.50) | 0.398 | | |
| Diabetes | 0.98 (0.54–1.75) | 0.948 | | |
| Smoke | 1.51 (0.86–2.67) | 0.150 | | |
| CKD | 1.93 (1.15–3.25) | 0.013 | 1.89 (1.13–3.15) | 0.014 |
| COPD | 1.13 (0.59–2.15) | 0.703 | | |
| Previous stroke | 1.24 (0.51–3.04) | 0.656 | | |
| Ejection fraction | 0.99 (0.96–1.02) | 0.636 | | |
| Previous MI | 1.53 (0.78–2.98) | 0.211 | | |
| Previous PCI | 1.11 (0.59–2.06) | 0.739 | | |
| Previous CABG | 0.94 (0.34–2.60) | 0.918 | | |
| *Coronary variables* | | | | |
| Proximal LAD location | 1.45 (0.97–2.17) | 0.066 | 1.07 (0.71–1.64) | 0.692 |
| DS ≥ 50% | 1.04 (0.72–1.49) | 0.809 | | |
| RLD (mm) | 1.06 (0.82–1.37) | 0.390 | | |
| LL (mm) | 1.01 (1.00–1.03) | 0.013 | 1.00 (0.98–1.01) | 0.489 |
| MLD (mm) | 0.90 (0.66–1.24) | 0.538 | | |
| QFR ≤ 0.80 | 3.11 (2.26–4.45) | < 0.001 | 2.91 (1.94–4.36) | < 0.001 |

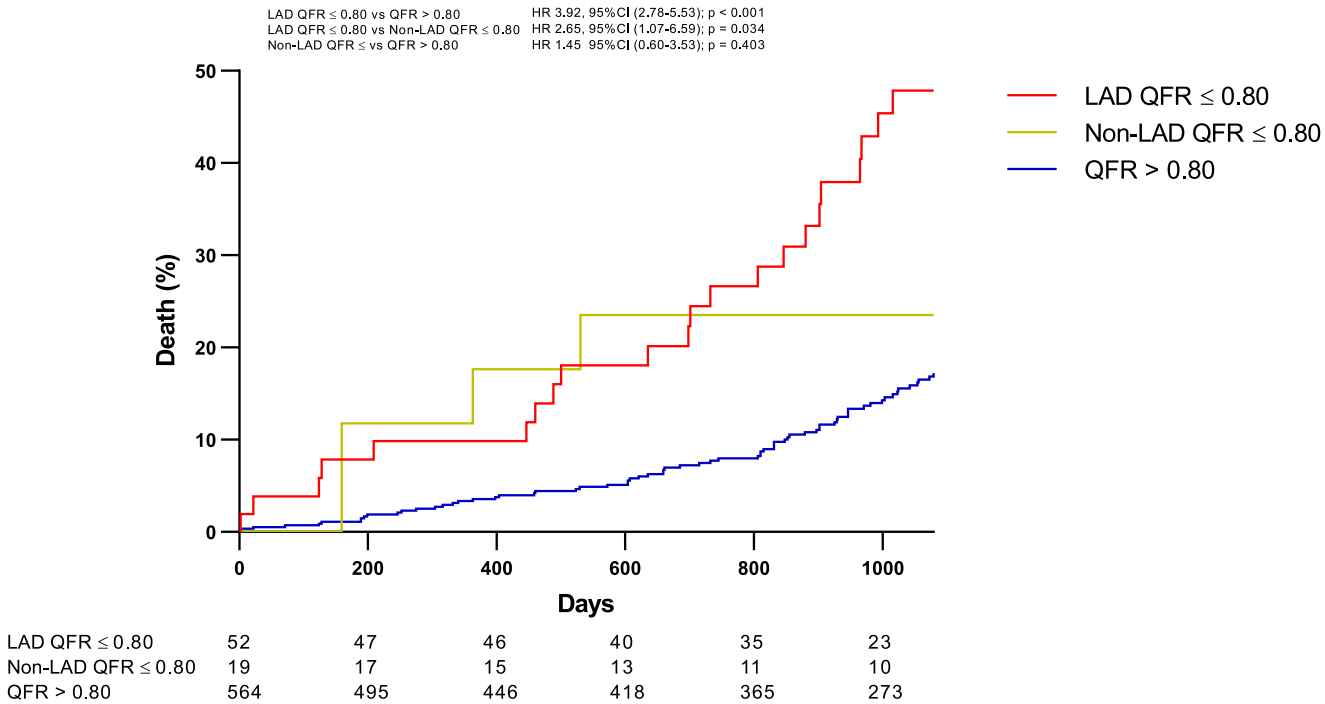


**FIGURE 4** | Mortality rates according to QFR-positive lesions' location. [Color figure can be viewed at wileyonlinelibrary.com]

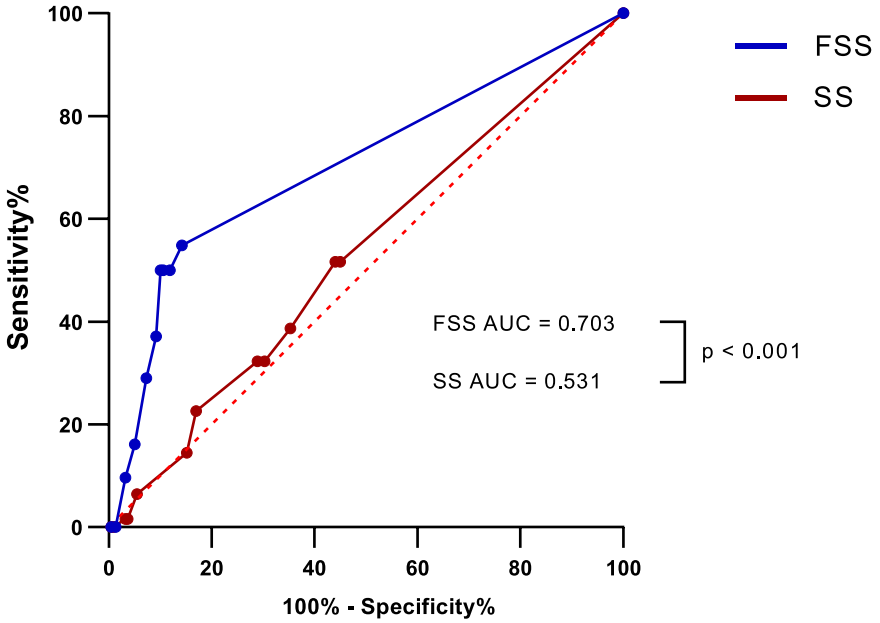


**FIGURE 5** | ROC analysis on the discriminative power for mortality of FSS and SS. [Color figure can be viewed at wileyonlinelibrary.com]

in a stable setting and, secondarily, to possibly improve outcomes. Under a similar perspective, the role of properly indicated revascularization deferral is crucial [30]. To date, it is unknown which are the deferring rates of QFR compared to both angiography and FFR in patients with AS, and further research is still needed.

Our work has several limitations. First, its retrospective nature and reduced sample size limit the generalizability of our findings. This could have particularly impacted the results of subgroup analyses, as the ones comparing the outcomes of QFR-positive lesions located at the LAD or non-LAD site. Second, no core lab assessment of angiographic data and clinical outcomes was performed. This, together with the exclusion of a significant proportion of patients due to the lack of angiographic data, may have introduced a significant selection bias. Third, only one clinical event was explored (mortality), while no insights were available on other significant outcomes such as MI, revascularizations, and cardiac deaths. This partially limits the validity of our vessel-oriented analysis, mainly because no speculations can be performed on the nature and causes of these death events. Moreover, the competing risk from non-cardiac causes of death (which are common in TAVR patients) could not be addressed as well. Fourth, for the same reason, vessel-level outcomes (which would have provided a more accurate depiction of our findings) were not available. Therefore, our data should be considered strictly hypothesis-generating. Fifth, the diagnostic accuracy of QFR compared to FFR in patients with AS was not assessed. Eventually, despite all included patients being managed medically, the decision on deferring or treating specific stenoses was originally left to the operators' discretion. Following our study should only be interpreted as a measure of the mortality risk correlated to QFR-defined CAD, and not as a prevalence study of CAD and death rates in patients undergoing TAVR.

In conclusion, QFR analysis of coronary stenoses in patients with AS undergoing TAVR leads to a significant reclassification of CAD at both patient- and vessel-levels. The risk of angiography/physiology mismatch is higher in large vessels and lesions located in the proximal LAD. QFR values are strictly associated with an increased risk of death at 3 years, especially in patients with LAD disease.


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### Disclosure

The authors have nothing to report.

### Conflicts of Interest

G.B.Z. has consulted, lectured, and/or served as advisory board member for Abiomed, Advanced Nanotherapies, Aleph, Amarin, AstraZeneca, Balmed, Cardionovum, Cepton, Crannmedical, Endocore Lab, Eukon, Guidotti, Innovheart, Meditrial, Menarini, Microport, Opsens Medical, Synthesa, Terumo, and Translumina, outside the present work. The other authors declare no conflicts of interest.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.
**Figure S1:** QFR values distribution. **Figure S2:** Correlation analysis between DS% and QFR. **Figure S3:** ROC analysis on the discriminative ability of DS% for QFR-positive lesions. **Table S1:** Relationship between death and QFR/angiography mismatch. **Table S2:** Multivariate analysis for mortality predictors (patient-level).