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Full Length Article

Prediction of hypofibrinogenemia and thrombocytopenia at the point of care with the Quantra® QPlus® System

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ABSTRACT

Introduction: Low fibrinogen and platelet counts are associated with bleeding and the need for transfusion. In this study, we investigated whether the Quantra® QPlus® parameters Fibrinogen Contribution (FCS) and Platelet Contribution (PCS) to clot stiffness could predict commonly used fibrinogen and platelet transfusion thresholds in patients undergoing major surgical procedures.

Methods: This study used data from a multicenter, prospective observational study of adult patients undergoing cardiac or major orthopedic surgery. Quantra and laboratory assays were performed in parallel at multiple time points. Logistic regression models were used to assess the ability of FCS and PCS to predict fibrinogen and platelet thresholds used to guide transfusions. Receiver operating characteristics (ROC) curves were analyzed to determine the diagnostic accuracy and the optimal FCS and PCS values corresponding to the laboratory-based thresholds.

Results: The areas under the ROC curves (AUCs) for FCS at fibrinogen thresholds of <120, 150, and 200 mg/dl ranged from 0.96 to 0.89. Similarly, for PCS at platelet thresholds of <50, 80, 100,000/μl, AUCs ranged from 0.95 to 0.89. The proposed optimal FCS and PCS cutoff values showed high negative predictive value and high sensitivity and specificity (both >86%) at the lowest fibrinogen and platelet threshold levels.

Conclusions: This study identifies potential cutoff values for QPlus FCS and PCS proposed for use in place of or in conjunction with laboratory-based assays fibrinogen and platelet thresholds to guide transfusion decisions in surgical patients. These cut-off values will need to be validated in future studies.

1. Introduction

Excessive perioperative bleeding is a multi-factorial complication frequently triggered by a combination of consumption, hemodilution, exposure to foreign surfaces, prolonged tissue trauma, and presence of anticoagulants, among others [1–3]. The management of perioperative bleeding requires a rapid assessment of coagulation status and identification of coagulation factor deficiencies to help guide targeted interventions with allogeneic blood products or factor concentrates.

Clinical practice guidelines for the management of coagulopathic bleeding in the perioperative and critical care settings recommend goal-directed therapy to restore balanced hemostasis [4–10]. Hypofibrinogenemia (fibrinogen values below 150 mg/dl) and thrombocytopenia (platelet count between 50,000/μl and 75,000/μl, or less) are associated with worsening coagulopathy and critical bleeding in cardiac and other major surgery, which warrants an immediate intervention. It has been demonstrated with viscoelastic testing assays that fibrinogen and platelets are some of the key contributors to clot rigidity and clot elastic properties, and that elevated fibrinogen levels can compensate for reduced platelet functionality induced by thrombocytopenia [11–13]. Furthermore, even though there is inter-patient variability, fibrinogen is often one of the first coagulation factors that is consumed and reaches critically low levels in major surgical procedures and/or with significant blood loss and in several goal-directed treatment algorithms it represents one of the first targets for intervention [14–17]. However, the practical implementation of treatment algorithms utilizing conventional assays of coagulation is often hampered by the slow turn-around time of results obtained from the central laboratory and the need to centrifuge samples.

The Quantra® QPlus® System (HemoSonics, LLC, Charlottesville,

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VA) is a Food and Drug Administration (FDA) cleared and CE marked point-of-care (POC) viscoelastic test (VET) device that outputs a series of functional parameters that characterize a patient's coagulation status. Output parameters include a series of clot times and clot stiffness values that represent the functional role of the major components of coagulation, including fibrinogen and platelets. The QPlus Cartridge parameter Fibrinogen Contribution to clot stiffness (FCS) has been previously shown to correlate with laboratory-based fibrinogen assays, whereas the Platelet Contribution to clot stiffness (PCS) parameter has been shown to integrate information about platelet number and platelet function [18–23]. A detailed description of the Quantra analyzer and the QPlus Cartridge parameters is presented elsewhere [18,19]. The performance of the Quantra QPlus System has been established in a series of clinical studies in cardiac and spine reconstruction surgery [18–25]. The results of these studies have demonstrated strong correlation and concordance of the QPlus parameters with other well-established VET technologies and the laboratory-based assays of coagulation.

In this study, we investigated whether the QPlus parameters FCS and PCS could predict fibrinogen and platelet transfusion thresholds associated with hypofibrinogenemia and thrombocytopenia in patients undergoing major surgical procedures. We hypothesized that QPlus parameters could provide rapid prediction of these conditions at the point of care.

2. Methods

The data presented here were obtained from a prospective observational study performed at four clinical sites in the United States between May 2017 and February 2018. The four participating clinical institutions were the University of Virginia Health System (Charlottesville, VA), Duke University Medical Center (Durham, NC), the University of Maryland Medical Center (Baltimore, MD), and the Medical University of South Carolina Health (Charleston, SC). The study was approved by each site's local Institutional Review Board and registered under Clinical Trial number NCT03152461. The work presented in this manuscript represents a new analysis and interpretation of the data previously collected in [21].

2.1. Patient population

The study involved 242 adult patients undergoing major cardiac and/or vascular procedures or major orthopedic surgery (primarily multilevel thoracolumbar spine surgery). In addition, a small number (n = 5) of subjects presenting with acute bleeding or suspected hypercoagulation in the post-surgical unit following cardiac, vascular or orthopedic surgery were also enrolled. Exclusion criteria included pregnancy, imprisonment, and inability to obtain consent. Preoperative use of anticoagulant or antiplatelet medications did not preclude enrollment in the study. Written informed consent was obtained from all enrolled subjects. Surgical patients' demographics are shown in Table 1 [21].

2.2. Testing protocol

Testing was performed at multiple time points before, during, and after the surgical procedures. At each time point, venous whole blood samples were collected by venipuncture or from an existing line into multiple citrated tubes (3.2% citrate) and one EDTA tube. The citrated tubes were analyzed with the Quantra QPlus System and in routine coagulation assays which included the measurement of fibrinogen levels using the Clauss assay. The EDTA tube was utilized for analysis of platelet count. All four clinical sites used automated fluorescent flow cytometry to measure platelet count (Sysmex; XN or XE analyzer with Fluorcell reagents). Measurements of fibrinogen via the Clauss assay were performed using two different types of multiparameter analyzers with different reagents, both of which are used interchangeably in coagulation laboratories worldwide (Instrumentation Laboratory, ACL TOP with HemosIL reagents; Diagnostica Stago, STA-R Evolution with STA reagents). The Clauss assay is currently the "gold-standard" for the measurement of functional fibrinogen levels and it is performed by measuring the clotting time of a plasma sample activated with high levels of thrombin. The Quantra QPlus Systems used in the study were labeled for Investigational Use Only (IUO). All the samples obtained from each enrolled patient were utilized for the data analyses presented here.

Table 1
Study demographics. Values are expressed as mean ± standard deviation or number (%).

	Cardiac and vascular patients		Major orthopedic patients	
Number of subjects	163		79	
Male sex n (%)	116 (71.2)		36 (45.6)	
Age (yrs)	62.7 ± 13.6		64.8 ± 11.4	
Weight (kg)	87.4 ± 20.6		90.5 ± 22.4	
Procedure	CABG	55	3–6 vertebral segments	22
	Valve repair or replacement	86	7–12 vertebral segments	19
	CABG/valve repair or replacement	6	13+ vertebral segments	11
	VAD	7	Other	27
	Other	9		
Surgery time (min)	302 ± 6		324 ± 10	
Preop medications				
Aspirin	150 (92%)		1 (1.3%)	
V-K antagonists	6 (3.7%)		0	
P2Y12 antagonists	8 (4.9%)		1 (1.3%)	
FXa inhibitors	5 (3.1%)		2 (2.5%)	
TXA	5 (3.1%)		9 (11.4%)	

2.3. Data analyses

All data analyses presented here were performed using either R Version 3.2.1 or higher (https://www.r-project.org/) or MATLAB version 9.6 with the Statistics and Machine Learning Toolbox version 11.5 (MathWorks Inc., Natick, MA). Linear regression analysis was performed to characterize the correlation between QPlus FCS and PCS vs fibrinogen level and platelet count, respectively. The strength of the correlation (r-value) was interpreted according to the following common definitions: 0.00 to 0.19 "very weak", 0.20 to 0.39 "weak", 0.40 to 0.59 "moderate", 0.60 to 0.79 "strong", and 0.80 to 1.0 "very strong" [26].

Logistic regression models were used to assess the performance of FCS and PCS in identifying fibrinogen and platelet thresholds typically used to guide transfusion decisions. Specifically, a logistic regression model with Firth estimation method was utilized to reduce small sample bias in maximum likelihood estimation [27]. Areas under the curves of the receiver operating characteristic (ROC) curves were calculated for each model and optimal cutoff values were obtained by using the Youden's J value. 95% Confidence intervals were estimated for cutoffs, sensitivity, specificity, negative and positive predictive values using a bootstrap technique with 1000 simulations.

3. Results

QPlus test results and routine coagulation test values were obtained from 163 subjects undergoing cardiac bypass surgery, 79 subjects undergoing major orthopedic surgery, and 5 patients presenting with acute bleeding, yielding a study dataset of approximately 800 distinct observations. Post-operative bleeding volumes at 6, 12, and 24 h after surgery

measured from the chest tube output were as follows: (cc, mean(SD)): 272(236), 421(283), and 679(438), respectively. Note that even though the QPlus Cartridge outputs a total of six parameters that describe the patient's coagulation status, this work focused specifically on the FCS and PCS parameters. Final FCS and PCS parameters were obtained within 12.6 ± 1.5 min of test initiation [21].

Table 2 summarizes the mean values for FCS, PCS, fibrinogen and platelet count as a function of time-point for the cardiac and major orthopedic surgery patients. As expected, mean values for each parameter were highest at baseline, and trended lower during surgery and immediately post-surgery.

3.1. Correlation analysis

Fig. 1 depicts the relationship between FCS levels and fibrinogen levels (top panel) and PCS levels and platelet count (bottom panel). Fibrinogen levels spanned from 63 mg/dl to >800 mg/dl and platelet count spanned from 21,000/μl to 464,000/μl across the patient population, hence covering ranges well below and above the respective reference range intervals. The linear correlation coefficient indicated strong correlation for both comparisons.

3.2. ROC analysis

ROC curves are presented in Fig. 2 for varying threshold levels of fibrinogen (top panel) and platelet count (bottom panel). The solid dot in each of these curves indicates the point of optimal combination between sensitivity and specificity based on the maximum value of the Youden's index. Point estimates of the areas under the curve (AUC) obtained from ROC analyses are presented in Table 3. The AUCs for FCS at fibrinogen thresholds of <120, 150, and 200 mg/dl ranged from 0.96 to 0.89. Similarly, for PCS at platelet count thresholds of <50,000, 80,000, and 100,000 per μl, AUCs ranged from 0.95 to 0.89.

Table 4 provides the optimal QPlus FCS and PCS cutoff values at each fibrinogen or platelet threshold analyzed with the corresponding specificity, sensitivity, negative and positive predictive values (NPV and PPV), respectively. The QPlus cutoffs identified demonstrated high NPVs and high sensitivity/specificity at the lowest fibrinogen and platelet threshold levels. Note that a platelet count below 50,000/μl was observed in only 5 instances across the study database.

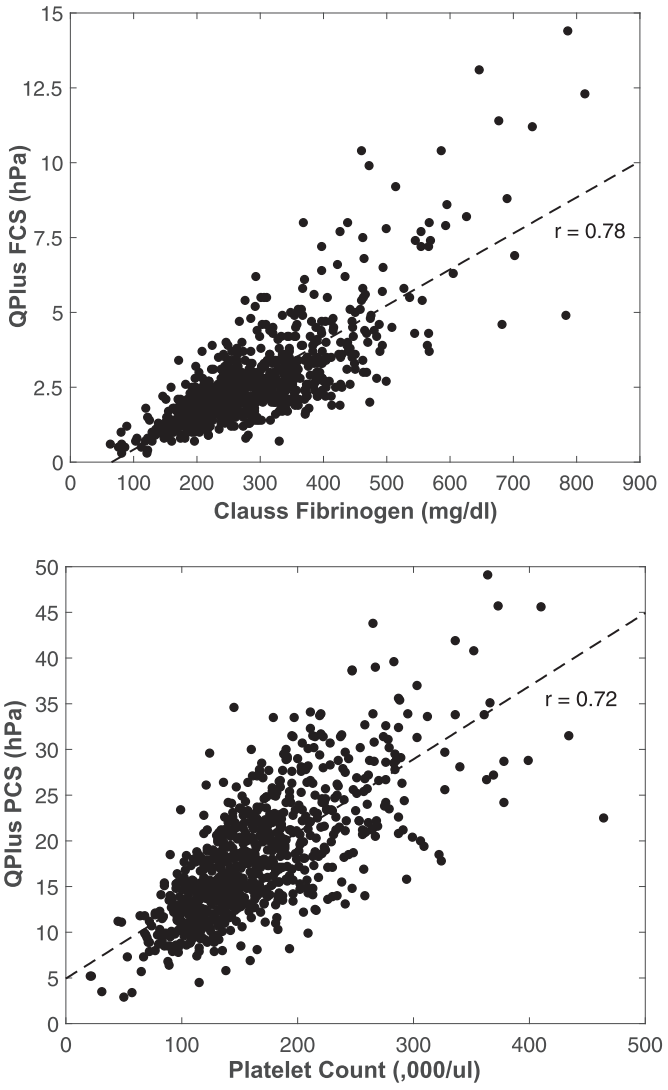

Fig. 1. Scatter plots depicting QPlus FCS vs fibrinogen level (top panel) and QPlus PCS vs platelet count (bottom panel). For each comparison, the linear best fit is shown as a dotted line with the corresponding Pearson r-value.

4. Discussion

Low fibrinogen and low platelet counts are associated with clinically significant bleeding and often require therapeutic intervention with allogenic blood products or factor concentrates. Perioperative and trauma guidelines recommend specific fibrinogen and platelet threshold values that should be targeted for interventions [4–10]. The Practice Guidelines for Perioperative Blood Management issued by the American Society of Anesthesiologists (ASA) recommend the utilization of platelet transfusion if the platelet count is less than 50,000/μl in the presence of bleeding [4]. Cryoprecipitate is recommended when the fibrinogen concentration is below 80–100 mg/dl in the presence of bleeding, but rarely indicated for levels greater than 150 mg/dl. The recent Society of Cardiovascular Anesthesiologists (SCA) and European EACTS/EACTA guidelines for cardiac surgery recommend utilization of fibrinogen replacement therapies (typically cryoprecipitate in the US and fibrinogen concentrate in Europe) if fibrinogen is below 150 mg/dl or platelet concentrates if platelet counts are below 50,000/μl in the presence of microvascular bleeding [7,8]. Similar recommendations are also

Table 2
QPlus' FCS and PCS, fibrinogen levels, and platelet counts across the study time points.

	Cardiac surgery				Major orthopedic surgery		
	Baseline	Bypass	Post-bypass	ICU	Baseline	Intra-surgery	ICU
FCS (hPa)	3.3 (2.3)	2.5 (1.4)	2.2 (1.4)	2.7 (1.4)	2.8 (1.7)	2.2 (1.0)	2.5 (0.9)
PCS (hPa)	20.8 (7.4)	16.5 (6.0)	16.1 (6.7)	17.6 (6.3)	20.7 (5.5)	19.6 (7.3)	18.0 (5.7)
Fibrinogen level (mg/dl)	336 (124)	233 (71)	225 (71)	329 (109)	318 (99)	247 (81)	327 (70)
Platelet count (,000/μl)	183 (54)	158 (49)	140 (53)	144 (51)	218 (66)	205 (72)	166 (62)

Values expressed as mean (standard deviation).
FCS: Fibrinogen Contribution to clot stiffness.
PCS: Platelets Contribution to clot stiffness.
hPa: hecto-Pascals.

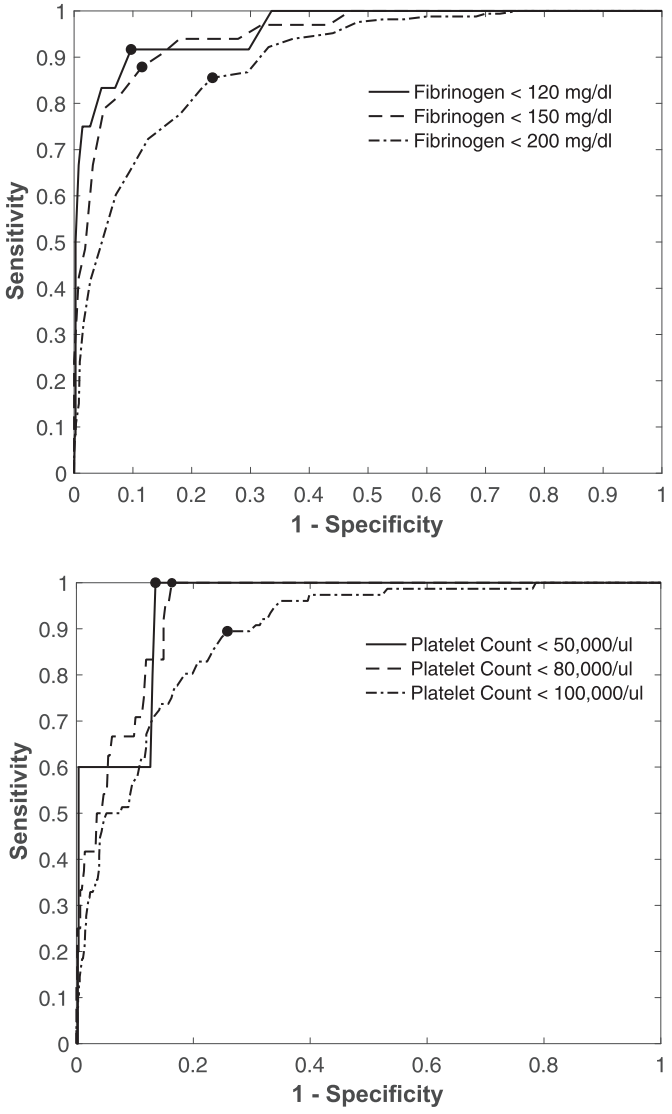

Fig. 2. Receiver-operating characteristic (ROC) curves showing FCS (top panel) and PCS (bottom panel) ability to predict varying levels of fibrinogen and platelet count, respectively. The Areas under the curve (AUC) are summarized in Table 3. Note that only 5 samples had platelet counts below 50,000/μl.

Table 3
Areas Under the Curves (AUC) of receiver-operating characteristic curves for different fibrinogen and platelet count threshold values.

	Fibrinogen level (mg/dl)		
	<120	<150	<200
FCS	0.96 (0.91, 1.00)	0.95 (0.92, 0.98)	0.89 (0.87, 0.92)
	Platelet count (per μl)		
	<50,000	<80,000	<100,000
PCS	0.95 (0.88, 1.00)	0.94 (0.92, 0.97)	0.89 (0.85, 0.92)

Values in parentheses represent the 95% confidence intervals.

proposed by the European Society of Anesthesiology (ESA), the European guideline on management of major bleeding and coagulopathy following trauma, and the Association of Anaesthetists of Great Britain and Ireland (AAGBI) [5,6,9,10].

In this multi-center study, we demonstrated that the FCS and PCS parameters reported by the Quantra QPlus System can reliably predict most critical levels of hypofibrinogenemia and thrombocytopenia in patients undergoing cardiac and major orthopedic surgery. With the QPlus Cartridge, FCS is measured as the clot stiffness of a sample activated with tissue factor and with inhibition of the platelet's GP IIb/IIIa receptor. PCS is calculated as a difference between the overall clot stiffness (CS) and FCS, as previously described [18,19,21]. It was recently demonstrated that the PCS parameter is independently associated with platelet count and ADP-dependent platelet function as measured by multiple electrode aggregometry [23]. Unlike the laboratory-based assays for fibrinogen levels and platelet count which measure discrete analytes, the QPlus FCS and PCS parameters are not measured in isolation and represent the physiological cross-functionality that exists between platelets and fibrinogen during coagulation.

The data presented in Fig. 1 show a strong correlation of the QPlus parameters and the corresponding laboratory assays. These correlations are in general agreement with results shown in other single-site studies in cardiac and major spine reconstruction surgery. Furthermore, the correlation of PCS with platelet count is in agreement with those of Barishnikova et al. [23]. In the case of FCS, both the QPlus and the laboratory fibrinogen assay measure the functional activity of fibrinogen, albeit FCS is derived from whole blood whereas laboratory fibrinogen is derived from plasma. The top panel of Fig. 1 also reveals that the dispersion of measurements from the best-fit line increases with increasing fibrinogen concentrations. It is hypothesized that this phenomenon is likely caused by varying hematocrit levels, as previously shown by Ogawa et al. [28]. For a fixed plasma concentration of fibrinogen, variations in hematocrit levels do impact the measured clot stiffness with low hematocrit generating higher stiffnesses. As the fibrinogen concentration increases this effect becomes more pronounced.

The strong correlations between QPlus parameters and laboratory values are aligned with the results of the ROC analyses presented in Tables 3 and 4, and Fig. 2 showing excellent sensitivity and specificity. These results are consistent with those previously presented by Engberink et al. [29] and Ogawa et al. [30] utilizing the ROTEM delta. The data indicate that cutoff values could be established for the QPlus FCS and PCS parameters as part of a goal-directed treatment algorithm for perioperative care. In addition to the high sensitivity and specificity, the FCS and PCS cutoff values demonstrated a high negative predictive value thus indicating that test results above these thresholds may rule out varying levels of thrombocytopenia and hypofibrinogenemia. Since the Quantra was designed to be operated at the point-of-care and provide results with a turn-around time of approximately 15 min, these results indicate that this new VET device has the potential to rapidly assess coagulation function and the need for transfusion.

This study was limited as the Quantra QPlus System was used observationally. Future studies should focus on the interventional utilization of the system to clinically validate the selection of the proposed cutoff values for guiding blood product use. Furthermore, only 5 observations across the study population had platelet counts below 50,000/μl. Despite the promising results presented here, the performance of PCS in the setting of very low platelet count (below 50,000/μl) should be further explored and the results presented here should be interpreted accordingly. Finally, it is important to recognize the limitations of the comparisons presented in this study. While QPlus' FCS and PCS are functional parameters measured in whole blood, the Clauss fibrinogen level is measured in plasma and the platelet count does not offer functional information.

In conclusion, this study identifies potential cutoff values for the Quantra QPlus parameters FCS and PCS proposed for use in place of or in conjunction with laboratory-based fibrinogen and platelet thresholds to guide transfusion decisions in surgical patients.

Table 4
Threshold, sensitivity, specificity, positive and negative predictive values for different fibrinogen and platelet count threshold values.

	Fibrinogen (mg/dl)			Platelet count (per μl)		
	<120	<150	<200	<50,000	<80,000	<100,000
	N = 12	N = 33	N = 166	N = 5	N = 24	N = 76
Proposed QPlus cutoffs (hPa)	FCS < 1.2	FCS < 1.3	FCS < 1.9	PCS < 11.2	PCS < 12.1	PCS < 14.1
	(0.9, 1.7)	(1.0, 1.6)	(1.7, 2.2)	(8.7, 15.0)	(11.8, 12.7)	(12.6, 16.0)
Sensitivity (%)	91.7	87.9	85.5	100	100	89.5
	(77, 100)	(73.9, 95.6)	(76.7, 97.2)	(100,100)	(98.8, 100)	(79.0, 100)
Specificity (%)	90.3	88.4	76.5	86.5	83.7	74.2
	(77.0, 100)	(79.6, 98.5)	(64.3, 84.5)	(78.0, 92.7)	(79.8, 86.4)	(61.0, 83.7)
PPV (%)	12.8	25	49.3	4.5	16	26.8
	(1.5, 28.9)	(14.5, 50.0)	(38.9, 59)	(3.7, 55.6)	(10.2, 22.4)	(18.1, 35.1)
NPV (%)	99.9	99.4	95.2	100	100	98.5
	(99.6, 100)	(99, 100)	(92.7, 98.2)	(100, 100)	(100, 100)	(97.2, 99.8)

Values in parentheses represent the 95% confidence intervals.
PPV – Positive Predictive Value.
NPV – Negative Predictive Value.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ramu G. Sudhagoni and Francesco Viola are employees of HemoSonics, LLC, a medical device company that is commercializing the Quantra QPlus System.

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