RESEARCH ARTICLE

REVISED Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension: A retrospective study of 75 paediatric cases [version 2; peer review: 2 approved with reservations]

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Abstract

Background: Ventricular septal defects (VSD) are the second commonest congenital heart defects after bicuspid aortic valve. When left unrepaired, they can undergo spontaneous closure or elicit a spectrum of complications including pneumonia (PNA) or pulmonary hypertension (PH) with subsequent anaemia. In this retrospective study, we aim to establish and compare the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods: A total of 75 case files of patients with solitary acyanotic VSD, who underwent surgical closure or device occlusion had haemoglobin level analysed prior to the procedure. The cohort included patients with (history of) PNA and PH, and asymptomatic. The cohort included 27 females and 48 males with mean age and weight of 8.3 ± 5.72 (3-24) months and 5.9 ± 3.9 (2.7-17.8) kilograms, respectively. Depending on associated complication and age, the cohort was divided: PNA (A), PH (B) and Control (C); and (I) young children ($\geq 3-6 \leq$) and (II) older children ($>6- \leq 24$) months. We used 95 and 105 grams per litre as haemoglobin lower threshold level for (I) and (II), respectively.

Results: According to data analysis 27 patients (36%) in total had anaemia. Of the anaemia cohort 16 (59.3%) had PNA, 9 (33.3%) PH and 2 (7.4%) were asymptomatic. Of the cohort, 42 were young children, with anaemia prevalence of 19/42 (45.2%), while 24.2% of the older children had anaemia. Intergroup ANOVA independent sample t-test was significant ($p < 0.05$). In addition, intergroup *Tukey HSD* test for haemoglobin: A/B ($p > 0.05$), A/C ($p < 0.01$), B/C ($p < 0.01$).

Conclusion: Paediatric patients with acyanotic VSD in comorbid with

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Approval Status ? ?

	1	2
version 2		
(revision)		
19 Nov 2019	view	view
version 1		
25 Jan 2019	view	view

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2. **Raymond N. Haddad** , Saint Joseph University, Beirut, Lebanon

Any reports and responses or comments on the article can be found at the end of the article.

PNA or PH are 8 and 4 times more susceptible to develop anaemia compared to asymptomatic counterparts. Susceptibility is even higher among young children (3-6months). However, a prospective study is needed to validate our findings.

Keywords

Ventricular septal defect, Pneumonia, Pulmonary hypertension, Anaemia

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Author roles: **Changwe GJ:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Zhang H:** Methodology, Resources; **Li H:** Formal Analysis, Supervision; **Farhaj Z:** Data Curation, Methodology; **Tewara MA:** Formal Analysis, Software; **Zhang W:** Validation, Visualization; **Zou C:** Funding Acquisition, Project Administration, Validation

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

On behalf of co-authors, I wish to pass our heartfelt gratitude to the reviewer for his professionalism and sincerity, and the raised points deserve clarification. The main differences between the old and revised version are put forward as per reviewer concerns:

The introduction section has been summarized and repair techniques clarified with references.

Diagnosis modality of PH has been clarified and reference cited. While we understand the variation in etiologies of pneumonia, cardio-pulmonary hemodynamic changes provide a fertile ground for persistent infections (dereferences available).

SPSS version has been given in full.

Discussion has been expanded by two paragraphs and references provided.

Conclusion has been furnished.

We have changed the addresses to suit institutional requirement. Its our sincere hope that our revised version answers the few but cardinal concerns raised by our reviewer.

Your time and dedication to reviewing our manuscript is highly appreciated.

Any further responses from the reviewers can be found at the end of the article

Introduction

Anaemia is a common complication of a myriad medical conditions often met in general ward. Its etiology is complex and multifactorial, encompassing intrinsic and extrinsic factors¹⁻³. Additionally, large intracardiac defects (cyanotic ventricular septal defects) can cause pulmonary vascular overload, infection and anaemia². Further, pulmonary hypertension (PH) due to pulmonary vascular overload can elicit a cascade of events leading to poor quality of life, morbidity and mortality^{4,5}. In the developing world with no heart surgery centers, pneumonia (PNA) due to large intracardiac defect(s) (cyanotic VSDs) is responsible for retardation, persistent morbidity and mortality^{2,6}.

Nevertheless, the effect(s) of small to moderate VSD's on the occurrence of both PNA and PH amongst paediatric patients, especially infants has not been fully explored. Adults and older children may tolerate and survive the effects. However, infants with limited iron storage and supply (exclusive breast milk) may not with stand^{7,8}. For these reasons, we hypothesize that

paediatric patients with solitary acyanotic VSD coexisting with PNA or PH retain a risk of developing anaemia. In this retrospective study, we aim to establish the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH.

Methods

Case file details and classification

Between February 2014 and September 2018, 90 case files of patients with solitary acyanotic-VSD, who underwent either surgical or minimal invasive closure in our Department of Cardiac Surgery, Shandong Provincial Hospital Affiliate of Shandong University were primarily selected for this study.

However, only 75 case files met study criteria, which included patients with recurrent (history of...) pneumonia of proven PNA by chest radiography with positive bacterial culture of trans-tracheal aspirate or polymerase chain reaction from nasopharyngeal swab. Pulmonary hypertension diagnosis was echocardiography based, except in 5 patients from PNA group, who presented in heart failure state. Excluded from this study were 15 files of patients: 7, sickle cell; 4, β -Thalassemia; 4, blood transfusion.

Among the 75 files were 48 males (75.64%) and 27 females with mean age and weight of 8.3 ± 5.7 (3–24) months and 3.8 ± 3.0 kilograms, respectively. Depending on the associated complication, the cohort was then divided into three groups: A, PNA (n=30); B, PH (n=25); and C, control (n=20). Based on age, the cohort was further split into two groups: I, young children (≥ 3 – ≤ 6); II, older children (> 6 – ≤ 24) months. The patient demographic and clinic characteristics (Table 1) and hematologic profile (Table 2) reflects pre-procedure state.

Data variables

Statistical analysis. Data was analysed using SPSS-IBM-21 software (one-way-ANOVA) and all statistics expressed as mean $\pm$ standard deviation. Intergroup haemoglobin level was compared using independent samples student's t-test. Statistical comparison of proportions was analysed using *Tukey HSD Test*, and the probability value of less than 0.05 was considered significant. Patient proportions are expressed in number and percentage (n, %).

Table 1. Patient demography and clinical characteristics.

Variable	Total	Groups		
		A	B	C
N	75	30	25	20
Age, months, mean $\pm$ SD	8.3 $\pm$ 5.72 (range, 3–24)	10.8 $\pm$ 19	11.5 $\pm$ 12.8	8.8 $\pm$ 5.1
Gender (female/male)	27/48	9/21	10/15	8/12
Weight, kgs, mean $\pm$ SD	5.9 $\pm$ 3.9 (range, 2.7–17.8)	4.9 $\pm$ 3.2	6.5 $\pm$ 4.8	6.7 $\pm$ 3.4
Ventricular septal defect, cm, mean $\pm$ SD	0.93 $\pm$ 0.31 (range, 0.4–1.6)	1.2 $\pm$ 0.3	0.89 $\pm$ 0.2	0.65 $\pm$ 0.2
Pulmonary hypertension, mmHg, mean $\pm$ SD	25.5 $\pm$ 8 (range, 16–55)	21.2 $\pm$ 3.4	34 $\pm$ 8.2	21.4 $\pm$ 2.7

Results

In this case study, we used hemoglobin reference ranges based on age as follow: (I) young children (95–135) and (II) older children were (105–135) gram per liter, as per local protocol. According to data analysis reflected in Table 3, 27 patients (36%) in total had anaemia. Of the anaemia cohort, 16(59.3%) had PNA, 9 (33.3%) PH and 2(7.4%) asymptomatic. Of the cohort, 42 were young children with anaemia prevalence of 19/42(45.2%), while the older children had 24.2%. Hemoglobin Intergroup (ANOVA) independent sample t-test was significant ($p<0.05$). In addition, intergroup *Tukey HSD* test for hemoglobin: A/B($p>0.05$), A/C($p<0.01$), B/C($p<0.01$). The mean WBC in PNA was higher and intergroup p-value was significant. Other hematologic and laboratory are reflected in the respective group

Of the cohort, 42 were young children, and of those 19 had anaemia (45.2%), while 24.2% of the older children had anaemia. Haemoglobin intergroup (ANOVA) independent sample

t-test was significant ($p<0.05$). In addition, intergroup *Tukey HSD* test for haemoglobin: A/B ($p>0.05$), A/C ($p<0.01$), B/C ($p<0.01$). The mean white blood cells in patients with PNA was higher and intergroup p-value was significant ($p<0.05$).

Discussion

Anaemia, defined as haemoglobin (Hb) concentration below the 5th percentile for age at sea-level, is a common complication of a myriad medical conditions often met in the general ward¹. Its aetiology is complex and multifactorial, encompassing intrinsic and extrinsic factors. Both pneumonia (PNA) and pulmonary hypertension (PH) due to cyanotic congenital heart defect (CHD) have been implicated in the occurrence of anaemia^{2,3,6}. In addition, sporadic reports linking anaemia to PNA or PH amongst patients with acyanotic ventricular septal defect (VSD) have been publish.

VSD is the second commonest CHD after bicuspid aortic valve^{4,9}, and solitary cases account for almost 20%. One of the most

Table 2. Mean hematologic profile and laboratory results according to age groups.

Variable	Young children (≥ 3 – ≤ 6 months)			Older children (> 6 – ≤ 24 months)			p-value
	A*	B*	C*	A*	B*	C*	
Haemoglobin (g/l; mean $\pm$ SD)	109 $\pm$ 25.1	108.3 $\pm$ 21.2	132.2 $\pm$ 18	109.8 $\pm$ 25.8	117.9 $\pm$ 15.4	133.6 $\pm$ 6.8	*0.04 ^0.008
Mean corpuscular volume (f/l)	76.9 $\pm$ 7.3	85.7 $\pm$ 2.1	83.9 $\pm$ 9	74.6 $\pm$ 5	82.8 $\pm$ 6.6	85.6 $\pm$ 4.8	*0.001 ^0.0003
Mean corpuscular haemoglobin (pg; mean $\pm$ SD)	27 $\pm$ 3.1	30.3 $\pm$ 2.1	28.4 $\pm$ 1.8	33.9 $\pm$ 7.2	29 $\pm$ 2.9	30.4 $\pm$ 2	*0.006 ^0.039
Lactate dehydrogenase (mean $\pm$ SD)	236.8 $\pm$ 76.8	222.4 $\pm$ 61.6	213.6 $\pm$ 61.6	300.9 $\pm$ 119.2	174.3 $\pm$ 50	147 $\pm$ 30	*0.68 ^0.0001
White blood cell ($\times 10^9$ /L; mean $\pm$ SD)	12.5 $\pm$ 5.3	7.8 $\pm$ 2.4	6.9 $\pm$ 0.9	15.4 $\pm$ 5.7	6.7 $\pm$ 1.5	5.9 $\pm$ 2.1	*0.003 ^0.0001
Red blood cell ($\times 10^{12}$ /L; mean $\pm$ SD)	3.8 $\pm$ 0.9	3.6 $\pm$ 0.9	3.8 $\pm$ 0.4	3.2 $\pm$ 0.5	4.3 $\pm$ 0.6	4.8 $\pm$ 0.4	*0.9 ^0.0001

Table 3. Association between age and anaemia prevalence.

Group	N; age (months; mean $\pm$ SD)	Haemoglobin (%)	
		Anaemia	Normal
Young children (≥ 3 – ≤ 6 months; n=42)	19; 4.85 $\pm$ 1.07	45.2	54.8
Older children (> 6 – ≤ 24 months; n=33)	6; 12.69 $\pm$ 6.02	18.2	81.8
Association between complication and anaemia distribution			
		N (%)	
		Anaemia	Normal
A	16; 30	53.3	46.7
B	9; 25	36	68
C	2; 20	10	90

common defects associated with elevated pulmonary artery pressure is a large VSD. Elevated pulmonary artery pressure in CHD can be due to pulmonary hyper-circulation, pulmonary vasoconstriction, and pulmonary vascular disease, either alone or in combination. In an infant, despite pulmonary pressure being at systemic level, pulmonary vascular resistance is low; therefore, minor shunt easily elicits hyper-circulation^{2,4,6,10}.

PH, defined as mean pulmonary artery pressure of ≥ 25 mmHg at rest as measured by cardiac catheterization in children aged ≥ 3 months, is a serious disorder with a high morbidity and mortality rate². Blood shunt may cause haemolysis due to shear stress and produce free haemoglobin, which in turn depletes nitric oxide leading to endothelial dysfunction, vasoconstriction, pulmonary oedema and hypoxia. Furthermore, haemolysis produces arginase, which converts L-arginine to ornithine; therefore, bypassing nitric oxide production^{2,8,11}.

PNA as defined by Ozdemir and colleagues is a serious reason for morbidity and mortality in children (≤ 2 years) with hemodynamic significant VSD^{5,12}. Both PNA and PH share a common interface; inflammation, homostasis, hypoxia, and subsequent upregulation of erythropoiesis^{7,13}. Prolonged upregulated erythropoiesis in young children with low iron store and limited iron supplement leads to anaemia¹. In addition, microangiopathic hemolytic anaemia in CHD and PH has been reported³, a complication commonly observed in primary PH. Unlike in PH, *Mycoplasma Pneumonia* and *Plebsiella* are known to cause anaemia in PNA^{14–16}.

This study shows that acyanotic VSD within mean sizes: 1.2 ± 0.3 and 0.89 ± 0.2 centimeters, thus, defect measured from the left ventricular septal side are prone to pulmonary vascular infection/dysfunction. Both transthoracic and transoesophageal echocardiography were employed in the diagnosis and delineation of VSD and PH¹⁷. Although, right heart catheterization (RHC) is regarded as gold standard, our center favors echocardiography due to less vascular and technical challenges, especially in clinically compromised infants. According to 2018 guidelines issued by British Society of Echocardiography, aforementioned is recommended and RHC superiority is insignificant¹⁸. Young infants (3 months old) with small defects were considered for closure if defect(s) showed no trait of spontaneous closure in the presence of symptoms after 2 consecutive follow-up at 2-month interval. Apical VSDs (Swiss cheese) seldom achieved closure, hence, inclusion.

Although this study is not focused on closure techniques, suffice to mention that surgical and minimally invasive, i.e. 1. perventricular¹⁹, 2. peratrial²⁰ and 3. percutaneous ($< 10\%$) device closure were used. Surgical was employed when device implantation proved futile, while percutaneous was limited to a small portion due to vascular limitation and possible complications. Recent publication cited small weight and age as recipe for complication during percutaneous intervention²¹. In addition, surgical technique was employed with utmost care due to bypass related complication and blood transfusion complications related in PH subjects. Its worthy mentioning that this study does not include prevalence of anaemia post intervention. Symptomatic subjects became asymptomatic at dismissal, and both aforementioned and asymptomatic ones progressively improved anthropometric parameters during sequential follow-ups²².

Conclusion

Paediatric patients without hematologic disorders, diagnosed with hemodynamic significant acyanotic VSD in comorbid with pneumonia or pulmonary hypertension are 8 and 4 times susceptible to develop anaemia compared to asymptomatic counterparts. Susceptibility is even high amongst young children (3–6 months). However, a long post closure follow-up study is required to exclude possibly missed intrinsic (genetical/gastro-intestinal) and extrinsic (economical) etiologies and validate findings.

Ethical considerations

The Shandong Provincial Hospital Ethics Committee approved this study, and waived individual patient consent as the study was based on archived data.

Data availability

Harvard Dataverse: Anaemia in solitary acyanotic ventricular septal defect in comorbid with pneumonia or pulmonary hypertension; a retrospective study of 75 paediatric cases, <https://doi.org/10.7910/DVN/2B328D>²².

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Current Peer Review Status: ? ?

Version 2

Reviewer Report 05 December 2019

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Raymond N. Haddad

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- The entire article must be **grammatically reviewed** (however I can't propose corrections as I don't have the article lines numbered):
 - A lot of pleonasm.
 - A lot of misspelled words.
- Information that should be mentioned in the methods:
 - Why did you only include patients with closed VSD? In other terms what were the exact indications of VSD closure in included patients? At what age VSD was closed?
 - How was hemodynamically significant VSD confirmed? TTE, hemodynamic evaluation?
 - More detail on the minimally invasive approach is needed.
- Did all patients with VSD and anaemia have anaemia diagnosis workup since authors said the 15 excluded patients had differential anaemia diagnosis? What was the sequence of actions?
- "Among the 75 files were 48 males (75.64%) and 27 females with a mean age and weight of 8.3 ± 5.7 (3–24) months and 3.8 ± 3.0 kilograms, respectively. Depending on the associated complication, the cohort was then divided into three groups: A, PNA (n=30); B, PH (n=25); and C, control (n=20). Based on age, the cohort was further split into two groups: I, young children (≥ 3 – ≤ 6); II, older children (> 6 – ≤ 24) months. The patient demographic and clinic characteristics ([Table 1](#)) and hematologic profile ([Table 2](#)) reflects a pre-procedure state." This paragraph should be in the results and not in the methods.
- The First-line in the results should be in the methods.
- Discussion paragraph 5: Why did TEE use for in VSD? What is the advantage of TEE over TEE?

- The statistical analysis section must be reorganized. Please find an example below:
'Statistical analysis.
Statistical analyses were performed using the Statistical Package for the Social Sciences Statistics (SPSS), version 21 for Macintosh (IBM, Armonk, NY). Categorical variables were reported as frequency and percentage. Continuous variables are represented as mean with standard deviation or median with the range depending on normality of distribution. Intergroup haemoglobin level was compared using independent samples student's t-test. Statistical comparison of proportions was analyzed using Tukey HSD test. A p-value < 0.05 was considered statistically significant. All reported p values are two-sided.'
- I don't recommend indexing with this form before all comments are addressed appropriately.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatrics, Pediatric cardiology, Pediatric interventionnal cardiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 02 December 2019

<https://doi.org/10.5256/f1000research.23523.r56775>

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Yimei Liao

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1. This is a small-size retrospective study with only 75 patients, which is not enough to support their conclusions.
2. In the previous review comments, we asked two questions:
 1. For the VSD patients with PNA or PH, does the increased incidence of anaemia have any influence on the therapy or clinical management?
 2. As the aetiology of anaemia is multi factorial, any intrinsic and extrinsic factors should be analysed in this article. This is crucial.

However, I didn't see any reply and revision to them. Major revisions are needed.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Fetal medicine, fetal cardiology.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Version 1

Reviewer Report 15 October 2019

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Raymond N. Haddad

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Firstly, I want to thank The Editorial Team of F1000Research for this opportunity to review the following manuscript.

I want to also thank the authors for recommending as a reviewer for their manuscript. Although this comparative concept is extremely new and interesting, I will generate candid comments which at times may seem overly critical. Please accept these criticisms in the positive spirit in which they are intended. I believe that the manuscript would be suitable for indexing if the comments/questions are addressed and appropriate changes made.

1. The authors in their Introduction largely reviewed the anemia and the contributing factors of PNA and PH which in large part are repeated in the discussion section. For that, I recommend that authors should summarize their introduction while briefly reviewing the role of VSD closure in the anemia (especially when all their patients had repaired defects either surgically or with minimal invasive approach).
2. Authors are encouraged to detail the method of defect repair. When is was performed? Is it early on diagnosis or later in time? The reason for closure especially in small defects? What do they actually mean by minimal invasive closure? Is it percutaneously or using a hybrid approach? Moreover, authors should explain why did they consider PNA as the only lower respiratory tract infection? And diagnosis of PHT should be more clearly detailed and if international guidelines were used reference must be cited. Additionally, where all patients screened for other possible hematological diseases to be excluded from the study?
Table 1 : What does the patients mean by VSD size? is it the LV entry or the RV exit? I advice

the authors to mention minimum and maximum values especially in each of the 3 groups for the PHT row as it may seem that some of Group A patients had PHT.

3. Statistics: SPSS version must be reported.
4. Table 1 and 2 should be briefly described in the results sections.
5. Table 3 must be just reported in the text.
6. The first 4 paragraphs of the discussion are pure literature review without any relevant discussion with the study results. In fact excessive review could impose more stratified results: should authors report the etiology on the PNA since they described the possible implications of infectious organisms in anemia. Therefore, discussion should focus in some part on the prevalence of anemia in **repaired** VSD (and if possible discussing the timing of closure and its possible effect of the results) while highlighting what has been previously written by the authors.
7. No changes are needed for the limitations and conclusions section.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatrics, Pediatric cardiology, Pediatric interventional cardiology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 27 March 2019

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1. The manuscript is a small-size retrospective study about the prevalence of anaemia in patients with solitary acyanotic VSD in comorbid with PNA or PH; they find that patients with acyanotic VSD in comorbid with PNA or PH were 8 and 4 times more susceptible to develop anaemia compared to asymptomatic counterparts.
2. For the VSD patients with PNA or PH, does the increased incidence of anaemia have any influence on the therapy or clinical management?
3. As the aetiology of anaemia is multifactorial, any intrinsic and extrinsic factors should be analysed in this article. This is crucial.
4. As mentioned above, it suggests that this article needs to be revised before accepting for indexing.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Fetal medicine, prenatal diagnosis of fetal malformations

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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