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PET/CT and Hypo-Fractionated Radiotherapy of Patients with Head and Neck Cancer

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Abstract

Positron emission tomography/Computer tomography (PET/CT) is a multi-modality imaging diagnostic technique that analyzes the uptake and retention of different radiopharmaceuticals by cells providing metabolic information on biochemical processes. PET/CT has been used for radiotherapy planning, providing useful information to the Radio-oncologist about the localization, size and metabolic activity of tumor lesions. In this paper, we show advantages of the 18F-FDG PET/CT respect to simple CT imaging for target volume delineation in patients with diagnosis of Squamous Head and Neck Carcinoma that has been scheduled to undergo a hypofractionated radiotherapy treatment. On ten studied patients, the target volume defined from PET/CT images was less extensive than those defined from simple CT images. In six patients the target volume was significantly less extensive and in two of them a new lymph node disease was reported, re-staging and corresponding target volume was also delineated with less extensive margins from PET/CT images. A greater accuracy in delineating the volumes and improving the distribution of doses in the planning of the radiant treatment in these patients was possible, allowing a high precision in the delivery of the prescribed dose to the target volume diminishing the maximum dose to the adjacent healthy tissues. In conclusion we show that the use of 18F-FDG PET/CT was superior than the simple CT as the primary modality of imaging for hypofractioned radiotherapy treatment planning in patients with Squamous Head and Neck Carcinoma.

Keywords

PET-CT, Hypofractionated Radiotherapy, Head and Neck Cancer

1. Introduction

Squamous cell carcinoma of the head and neck (HNCC) is the sixth most common cancer with an incidence of approximately 600,000 cases per year and 300,000 deaths per year worldwide [1] [2]. In Cuba, cancer of the larynx is the fourth cause in incidence [3]. It preferentially affects male patients older than 50 years and its main risk factors are smoking and excessive alcohol consumption. However, an epidemiological transition is currently observed due to an increased incidence of head and neck cancer associated with human papillomavirus infection. The most common histological type is squamous, covering more than 90% of cases [1].

The use of different imaging modalities is essential for the diagnosis treatment and follow-up of patients with HNCC. Computed tomography (CT) and magnetic resonance imaging (MRI) are the conventional diagnostic techniques (CDT) that provide a structural image and allow identifying changes in size and anatomical distortion. These images modalities are often used for target volume delineation however, in case of CT images due to low contrast of soft tissues hinders target volume delineation [4].

Positron emission tomography (PET) is a nuclear medicine imaging diagnostic technique that analyzes the uptake and retention of different radiopharmaceuticals by cells and provides metabolic information on biochemical processes. Improve the detection of tumor lymph node infiltration and distant metastasis with respect to CDT. It allows characterizing if the structural alterations are due to the tumor, to sequels of previous treatments or to other biological processes. Therefore, PET provides additional information which complements the CDT [5] [6].

The treatment of these tumors contemplates different alternatives, the main ones being surgery and radiotherapy associated or not with chemotherapy and/or biological therapies, depending on the tumor stage and the functional reserve of the patient [7]. Radiotherapy has a very well established role either in the exclusive treatment or as adjuvant treatment. It offers possible benefits for allowing the cure of the patient, the preservation of organ functionality, and its cost-effectiveness. The evolution of the radiant methods from the beginning conventional radiotherapy looks for to reduce to the minimum the exposition of healthy tissue neighbor to the tumor and to maximize the dose in the tumor [8].

The use PET/CT in HNSCC is increasingly widespread. It has been used for the radiotherapy planning, especially for unconventional treatments such as: hypofractionated radiotherapy, where the treatment time is decreased by increasing the daily dose obtaining a similar tumor response than conventional fractionation in HNSCC [9].

The purpose of this paper is to show advantages of the 18F-FDG PET/CT respect to simple CT imaging for target volume delineation in patients with diagnosis of HNSCC that has been scheduled to undergo a hypofractionated radiotherapy treatment.

2. Material and Methods.

2.1. PET/CT Image Acquisition for Hypofractionation Radiotherapy Planning of HNSCC

The ^{18}F-FDG images were acquired in a Philips Gemini TF64 PET/CT system at Nuclear Medicine and Molecular Imaging Department belonging to Oncology and Radiobiology Institute (INOR), La Habana, Cuba. The PET component is a 3D tomograph with time-of-flight (TFO) capability. The CT component of the Philips Gemini system is a 64 slices Brilliance tomograph. Each patient received 3.7 MBq/kg body weight of ^{18}F-FDG by intravenous injection. After 60 min post-administration the patient is positioned in supine position and immobilized using an individually customized head mask which is fixed to a rigid head-holder toenhance the positioning accuracy and to prevent movement during image acquisition. The head holder is then fixed to a Philips Gemini PET/CT Overlay plane couch (http://civcort.com). An initial scout view was used to define a region from skull to the clavicles. A helical CT scan was performed over the region defined with the scout view using the parameters 120 kVp, 120 mAs, with pitch around 1, reconstructed slice thickness of 2.5 mm. The PET TOF emission data were acquired for 1.5 min/bed, with adequate bed number that lets includes with the acquisition FOV at maximum size in order to assure that patient shoulders were included in the image and the patient border could be delimited during the treatment planning. The CT was used for attenuation correction of PET data. The PET, CT slice reconstructions and spatial co-registration PET/CT were done with the Philips Extended Brilliance^{TM} Workspace (Philips, version 4.5.2.40008).

Patient data

Paired study was performed on patients who were irradiated with highly conformed techniques such as IMRT and received the dose in a hypofractioned form. A prospective, observational study was carried out in which 10 patients diagnosed in the Oncology and Radiobiology Institute (INOR) with loco-regional squamous cell carcinoma in pharynx, larynx and oral cavity included in the period between January-July 2018.

Inclusion criteria

1) Tumor classified as stage I-IV located in oropharynx, hypopharynx, larynx (not glottic stage I-II), or oral cavity according to the TNM classification of Malignant Tumors;

2) Histopathological diagnosis of invasive squamous cell carcinoma at the primary site;

3) Age > 18 years;

4) Informed consent according to the Helsinki declaration and local regulations;

5) The patient must be a candidate for external beam radical radiotherapy, and must be expected to complete the treatment;

6) World Health Organization (WHO) performance status of 0 - 2.

Exclusion criteria

1) Distant metastases;

2) The patient should not be in a state or have major co-morbidity that could be expected to influence the outcome of treatment, or interfere with the assessment of treatment outcome at follow-up, or (apart from the present disease) considerably reduce the life expectancy;

3) Patients who test positive for human immunodeficiency virus (HIV);

4) Prior surgical excision (except biopsy);

5) Planned (elective) surgery;

6) The existence of synchronous multiple malignancies (not leukoplakia) or previous history of cancer;

7) The patient must not be pregnant;

8) Socio-demographic or other factors that make it unlikely that the patient will be available for follow up of long term treatment outcome.

2.2. Target Delineation and Radiotherapy Planning

The spatial co-registered PET/CT images were transferred to Monaco radiotherapy planning system (5.11.02). The organs at risk (OAR) were delineated manually on CT images and target volumes (tumors and nodes) were delineated on both PET and CT images following the Gregory's guideline [10]. The sizes of target volume of interest (VoIs) drawn for tumor and node on both image modalities were calculated. The intra-patient absolute relative differences of VoI sizes were calculated.

The patients who fulfill the inclusion criteria described above received a hypofractionated radiotherapy treatment with a daily dose of 2.75 Gy (5 sessions/week) and 55 Gy as the total dose in the high-risk tumor target volume (CTV-Hi) while the low-risk tumor target volume (CTV-Lo) received a daily dose of 2.2 Gy (5 sessions/week) and 44 Gy as the total dose. The doses were delivered with the Modulated Intensity Technique (IMRT), performed in the radiotherapy planning system, Elekta Xio (Version 5.10). The treatment was delivered using an Elekta Synergy linac 2950. The patient position is verified weakly with a cone-beam tomographic image system (CBCT) coupled to the linac.

3. Results

As shown in **Table 1**, the most frequent age group of patients included in the study was between 55 - 70 years. All patients were male and 90% of them with toxic habits (cigar and alcohol) (**Table 1**).

The most frequent site of the primary tumor was the Oropharynx (80%) and 90% of the patients were at the locally advanced stage of the disease at diagnosis III and IVA.

Impact of Target Delineation Using PET/CT Images

The metabolic images obtained with the use of the 18FDG-PET-CT when being fused with the planning CT for the radiotherapy facilitated the design of the targets

Table 1. Demographic and clinical patients characteristic.

Patients	Sex	Age	Toxic Habit	TNM	Stage	Site
1	Male	55	yes	T2 N2b M0	IVA	tonsil
2	Male	67	yes	T2 N3 M0	IVB	tonsil
3	Male	60	yes	T2 N0 M0	II	tonsil
4	Male	56	yes	T3 N2a M0	IVA	tonsil
5	Male	52	yes	T4a N2b M0	IVA	tonsil
6	Male	71	yes	T3 N0 M0	III	tonsil
7	Male	66	yes	T2 N2a M0	IVA	base of tongue
8	Male	41	yes	T3 N1 M0	III	tongue
9	Male	42	Non	T2 N1 M0	III	tonsil
10	Male	66	yes	T4a N1 M0	IVA	tonsil

volume in these patients to which they had to plan a higher dose rate daily than those in conventional treatments (**Figure 1**).

The variability of the target volume was evident, with relative differences of up to 33% for the GTV tumor and 94% for the nodes GTV demonstrating the limited information of the tomography studies when they are used as the only modality in the design of the same being improved with the use of the PET-CT hybrid as shown in **Table 2**.

In six of the patients, the clinical-radiological diagnosis was much more extensive than the metabolic labeling and in two lymph node disease was not previously described (**Figure 2**), allowing us to re-staging them, delineating the volumes to be treated with less extensive margins and performing highly conformal treatments such as intensity modulated radiotherapy (**Figure 3**).

With the use of PET/CT we were able to obtain high precision in the delivery of radiotherapy, adjusting the prescribed dose to the target volume, decreasing the dose to adjacent healthy tissues as much as possible.

4. Discussion

The oncology has experienced in recent years a breakthrough in their treatments and therefore in their results. Similarly, images in general and those modalities used in oncology have also undergone a great development, being able not only to establish a morphological diagnosis, but a functional substrate, both through intrinsic properties of each tissue and the response of these to varied therapies. For example, PET corresponds to a functional image modality whose utility depends on the tracer we use.

Head and neck tumors have been selected as an especially interesting model to detect the value added by PET, given the complexity of their anatomy and the presence of numerous normal structures with variable uptake intensity of FDG^{18} [11].

In theory, PET-FDG can influence the planned volume of radiotherapy

Table 2. Volume size delineation by CT and PET/CT.

Patient	Volume GTV/Tumor			Volume GTV/Node		
	CT	PET/CT	Relative Difference	CT	PET/CT	Relative Difference
	(cm^3)	(cm^3)	(%)	(cm^3)	(cm^3)	(%)
1	25.99	22.89	13.54%	32.24	36.68	12.12%
2	34.00	35.75	4.88%	63.53	32.63	94.72%
3	32.76	30.40	7.75%	-	10.00	-
4	43.12	32.27	33.63%	21.76	14.33	51.83%
5	47.02	45.62	3.06%	37.11	23.82	55.78%
6	36.56	27.72	31.90%	-	11.31	-
7	37.52	35.21	6.56%	35.01	33.79	3.60%
8	40.29	39.86	1.08%	22.55	22.32	1.00%
9	33.75	32.18	4.87%	15.25	18.00	15.29%
10	48.35	44.10	9.64%	22.90	17.59	30.18%

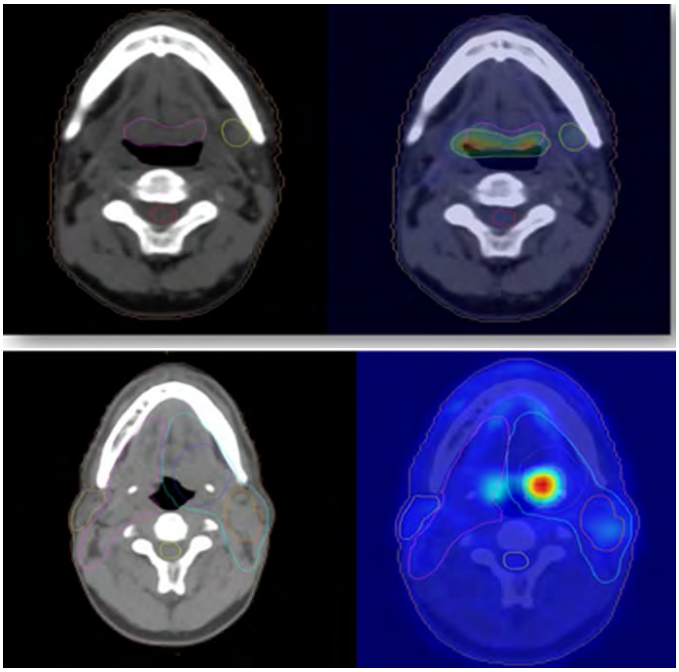

Figure 1. Delineated Volume in Planning CT vs. PET/CT.

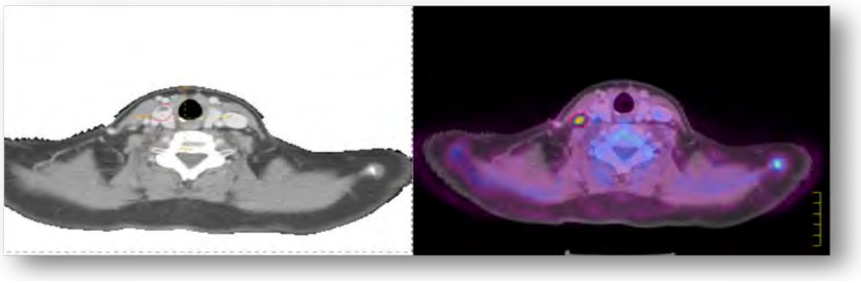

Figure 2. Positive Node identified in the PET image.

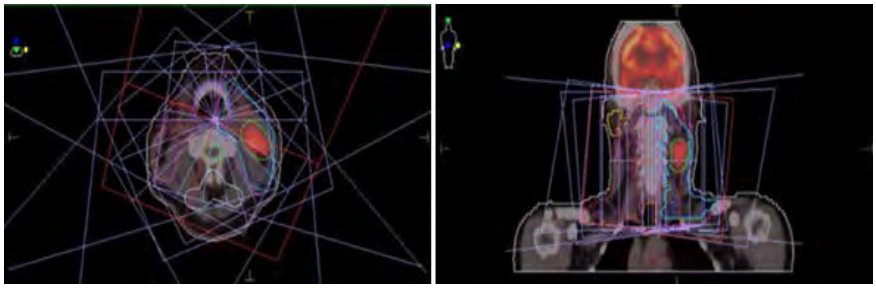

Figure 3. IMRT technique in merged CT and PET/CT image.

treatment and provide a dose reduction on healthy tissue. Facilitating the increase of the dose in the target volume to be treated [12].

According to Daisne *et al.*, the GTV delineated from 18F-FDGPET applying an adaptive signal-to-background method was significantly smaller than GTV delineated by CT or MRI. In addition, GTV-PET was the closest volume to the pathological GTV obtained from surgical specimen. On average, the PET delineated smaller volumes than CT or MRI [13].

Data from the literature reveal an increase in detectable tumor volume (GTV) in up to 20% of cases if PET/CT is used against CT. Numerous studies evaluate the information provided by PET-FDG in the planning of radiotherapy [14]. As it happened in two of our patients who were detected lymph node disease not previously reported.

In a recent multicentric prospective study by Leclerc *et al.*, the primary tumor was automatically delineated on the 18F-FDG-PET images using a gradient-based method previously described by this group. They confirmed that the use of 18F-FDG-PET smaller GTV, clinical target volume and planning target volume for the primary tumor volumes compared with the use of CT, lowering the dose to organs at risk [15] as it happened in the majority of our patients.

Deniaud-Alexandre *et al.*, in a retrospective study, confirmed that PET-CT has an impact on treatment planning and patient management. In this study, with a total of 101 patients, PET-FDG identified occult metastases in 8 patients (8%), and GTV decreased, with the fusion of PET-CT images, in 21 patients and increased in 24 patients. The reduction of GTV was >25% in 7 patients (7%) because PET-CT image fusion reduced GTV in 6 patients. The increase in GTV was >25% in 14 patients (14%) due to an increase in GTV in 11 patients [16].

Thus, in Spain, the Health Technology Assessment Agency has carried out an excellent systematic review and a meta-analysis on the indications of the PET-CT. Of 209 articles initially selected, only 16 could be used for the meta-analysis. Of these, 12 were prospective studies and 4 were retrospective, and there was a great variety of types of PET-CT, with different tumors studied and several indications of the procedure. In the specific study, the PET-CT provided an aggregate sensitivity of 0.85 (95% CI, 0.74 - 0.92) and an aggregate specificity of 0.84 (95% CI, 0.70 - 0.93). For the tumor re-staging, the sensitivity of the PET-CT was 0.89 (95% CI, 0.84 - 0.94) and the specificity 0.87 (95% CI, 0.78 -

0.93). The authors concluded that this combined technique is a useful technology in tumor staging and re-staging, because it increases the level of confidence in the diagnosis by decreasing the number of equivocal or inconclusive lesions [17].

5. Conclusions

18F-FDG PET/CT shows a significant impact on the management of patients with HNSCC on hypofractionated radiotherapy for target volume delineation increasing the visibility, precision in the design and planning in relation to the simple CT as primary imaging modality.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Meta-Analysis of Ventilated versus Spontaneously Breathing Patients in Predicting Fluid Responsiveness by Inferior Vena Cava Variation

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Abstract

Purpose: Respiratory variation in inferior vena cava (ΔIVC) has been extensively studied in predicting fluid responsiveness, but the results are conflicting. We performed a systemic review and meta-analysis of studies aiming at investigating the diagnostic accuracy of ΔIVC in predicting fluid responsiveness. **Methods:** MEDLINE, EMBASE, Cochrane Database and Web of Science were screened for relevant original and review articles from inception to July 2016. The meta-analysis determined the pooled sensitivity, specificity, diagnostic odds ratio (DOR) and area under the ROC curve (AUROC). In addition, subgroup analyses were performed in mechanically ventilated patients and spontaneously breathing patients. **Results:** A total of 20 studies involving 635 patients were included. Cutoff values of ΔIVC varied from 12% to 42%, the pooled sensitivity and specificity was 0.68 (0.62 - 0.75) and 0.80 (0.75 - 0.85), respectively. The DOR was 14.2 (6.0 - 33.6) and the AUROC was 0.86 (0.78 - 0.93). Subgroup analysis showed better diagnostic performance in patients on mechanical ventilation than in spontaneously breathing patients with higher sensitivity (0.75 vs. 0.56), specificity (0.82 vs. 0.78), DOR (22.9 vs. 7.9) and AUROC (0.90 vs. 0.80). The best threshold of ΔIVC in patients on mechanical ventilation was IVC distensibility index (ΔdIVC ≥ 17% ± 4%), compared to IVC collapsibility index (ΔcIVC ≥ 33% ± 12%) in spontaneously breathing patients. **Conclusion:** ΔIVC is not an accurate predictor of fluid responsiveness in patients with acute circulatory failure. In patients on mechanical ventilation, the predicting ability of ΔIVC was moderate with acceptable sensitivity and specificity; in spontaneously breathing patients, the specificity remains acceptable but its sensitivity is poor.

Keywords

Fluid, Responsiveness, Inferior Vena Cava Variation

1. Introduction

Hypovolemia is a very frequent clinical situation in the intensive care unit (ICU) and is primarily treated with volume expansion (VE). The only goal of VE is to improve the cardiac output (CO) of the patients especially those with acute circulatory failure [1]. However, multiple studies have demonstrated that only approximately 50% of hemodynamically unstable patients respond to VE in the ICU [2]. It is therefore essential to have reliable tools to predict the efficacy of VE and ultimately distinguish patients who may benefit from VE from those who are unlikely to respond. Recently, many studies have focused on the prediction of fluid responsiveness. Static hemodynamic indices have been of little value in predicting fluid responsiveness [3] [4]. In contrast, dynamic indices, based on analysis of preload dependence, have been validated as factors that can help predict fluid responsiveness [3] [5] [6] [7]. However, because of invasiveness and high cost, the application of these indices is of limited use in emergency rooms and general wards.

Bedside point-of-care ultrasonography has gained considerable attention because of noninvasiveness, rapid diagnosis and low cost [8]. The diameter of the inferior vena cava (IVC) is easily recorded by transthoracic echocardiography (TTE) in a subcostal view. Because of the heart-lung interactions, the maximum IVC diameter (IVCmax) and minimum IVC diameter (IVCmin) can be measured during thecycle of breath. Then, a term named respiratory variation in IVC diameter (ΔIVC) can be calculated. In recent years, intensivist had increasing interesting on ΔIVC for predicting fluid responsiveness.

Following the first study demonstrating the accuracy of the ΔIVC, it has been extensively investigated for its usefulness. In 2014, a meta-analysis pooling eight studies published at that time confirmed that ΔIVC is of great value in predicting fluid responsiveness [9]. However, since this meta-analysis, conflicting findings on its accuracy have been reported in a number of publications.

In order to clarify these mixed results and assess the ability of ΔIVC to predict fluid responsiveness, we conducted a systemic review of all these studies and performed a meta-analysis, with hypothesis that ΔIVC performs well in predicting fluid responsiveness.

2. Materials and Methods

2.1. Clinical Research Question

The clinical research question was: What is the sensitivity and specificity of the ΔIVC when using it to predict fluid responsiveness?

2.2. PICO Statement [10]

The PICO statement is as the following:

P-patient, problem or population: patients with acute circulatory failure in whom the effect of volume expansion (VE) is unknown and needs to be predicted.

I-intervention: Inferior vena cava (IVC) diameter was examined subcostally and measured in M-mode or 2D mode, 2 cm before the IVC joined the right atrium. The IVC respiratory variation (ΔIVC) was calculate by recordingthe largest and smallest IVCdiameter at end-inspiration or end-expiration.

C-comparison, control, and comparator: Fluid responsiveness was defined as a significant increase of stroke volume (SV), cardiac output (CO) or other surrogates during a VE.

O-outcomes: Ability of the ΔIVC to predict fluid responsiveness.

2.3. Searching Strategy, Study Identification and Data Extraction

Our aim was to identify all studies evaluating the ability of the ΔIVC to predict fluid responsiveness compared to the increase in SV, CO or other surrogates induced by subsequent VE.

We searched the MEDLINE, EMBASE, Cochrane and Web of Science databases for relative studies published in English from inception to July 2016. The key words we used consist of term related to IVC ("inferior vena cava", "caval index", "collapsibility" and "distensibility") and terms related to volume status ("fluid or volume or preload responsiveness", "fluid or preload challenge", "preload dependence or independence or dependency or independency", "functional haemodynamic monitoring" and "fluid therapy or management"). These key words were searched separately by two groups using different combination strategy. We also looked for relevant articles cited in review articles, commentaries and editorials. The search was performed repeatedly until no new studies could be found.

Study identification was performed in two steps. Step 1 comprised screening for titles and abstracts, and step 2, review of full texts of studies obtained in step 1. We only included studies investigating the accuracy of the ΔIVC that were published in full text or accepted for publication in indexed journals. Excluded criteria were 1) studies using central venous pressure or right atrial pressure as the reference standard, because these static parameters cannot predict fluid responsiveness accurately; 2) studies measuring IVC with techniques other than ultrasonography; 3) studies involving animals and healthy volunteers. Two reviewers process searching independently, disagreement was settled by a third opinion. The quality of the included studies was evaluated by using the QUADAS-2 scale [11]. The meta-analysis was performed according to the PRISMA statement.

Important information was extracted from the included articles using a standardized data form by two reviewers. Extracted data include the name of the first

author, publication year, characteristics of the investigated population, sample size, respiratory pattern, the device for IVC measurement, formula for the calculation of ΔIVC, definition of fluid responsiveness and volume challenge strategy, the number of true positives, true negatives, false positives and false negatives, sensitivity, specificity, the area under the receiver operation characteristics curve (AUROC) and the best threshold of ΔIVC which is used to predict the fluid responsiveness.

2.4. QUADAS-2 Quality Assessment in Included Studies

Included studies were assessed for their quality based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) protocol. QUADAS-2 scale [11] was made up of 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. For the "patient selection" domain, we examined whether patients were consecutively included and whether inappropriate exclusions were avoided. For the "index test" domain, we examined whether the threshold used to define volume responsiveness was pre-specified. For the "reference standard" domain, we examined whether the result of VE on SV, CO or surrogates was assessed without knowledge of ΔIVC result. Finally, for the "flow and timing" domain, the authors examined whether there was an appropriate interval between IVC measurement and VE, whether patients received the same VE and whether all patients were included in the analysis. For each criterion, the risk was judged as high, low and unclear.

2.5. Statistical Analysis

We performed a meta-analysis in order to determine the pool sensitivity, specificity and diagnostic odds ratio (DOR). In addition, the pooled area under the ROC curve (AUROC) and threshold for ΔIVC as a predictor of fluid responsiveness was also evaluated. To investigate a threshold effect, we calculated the Spearman correlation coefficient between sensitivity and specificity. Homogeneity between studies was tested by the Chi squared test and I^2 index. According to heterogeneity, we adopted a random effect model by using the method of DerSimonian-Laird from the Mantel-Haenszel model. We compared studies with ICU setting versus non-ICU setting making the hypothesis that ΔIVC could be more reliable in ICU patients. We compared studies with adults versus children making the hypothesis that ΔIVC could be more reliable in adults. We compared studies with different devices for measuring IVC making the hypothesis that one device is better than the others. We compared studies with three different formulas for the calculation of ΔIVC making the hypothesis that one formula is better than the others. We compared studies with patients on mechanical ventilation versus studies with spontaneously breathing patients, testing the hypothesis that the reliability of ΔIVC is better in patients on mechanical ventilation. We compared studies where fluid responsiveness was defined by an increase in SV,

CO or surrogate ≥ 15% versus studies with other definitions of fluid responsiveness, testing the hypothesis that the reliability of ΔIVC is better when fluid responsiveness is defined by a larger increase. We compared studies where SV, CO or surrogate were measured by echocardiography versus studies where they were measured by other methods, testing the hypothesis that the reliability of ΔIVC is better when SV, CO or surrogate were measured by echocardiography. Finally, we compared studies where VE was performed with versus studies where it was performed by colloids, testing the hypothesis that the reliability of ΔIVC is better when VE is performed with colloids. Causes of heterogeneity were also investigated by meta-regression based on the Littenberg and Mose linear model.

Results are expressed as mean (95% confidence interval) or as mean ± standard deviation. The meta analysis was performed with Meta-Disc v.1.4 (Universidad Complutense, Madrid, Spain). The additional statistical analysis was performed with MedCal 15.2.2 (MedCal Software, Mariakerke, Belgium). A two-tailed $p < 0.05$ was considered to statistical significance.

3. Results

3.1. Characteristics of Included Studies

A flow chart of the study selection is provided in Figure 1. Our initial search identified 399 citations. 379 of them were excluded: 320 for not relating to the subject, 49 for being reviews, letters, guidelines, case reports and editorials, 3 for not writing in English, 4 for not using proper reference standard, 3 for being animal experiments. Finally, a total of 20 studies [12]-[31] reported the ability of ΔIVC to predict fluid responsiveness were included in our analysis.

Characteristics of included studies are listed in Table 1. Sample sizes were

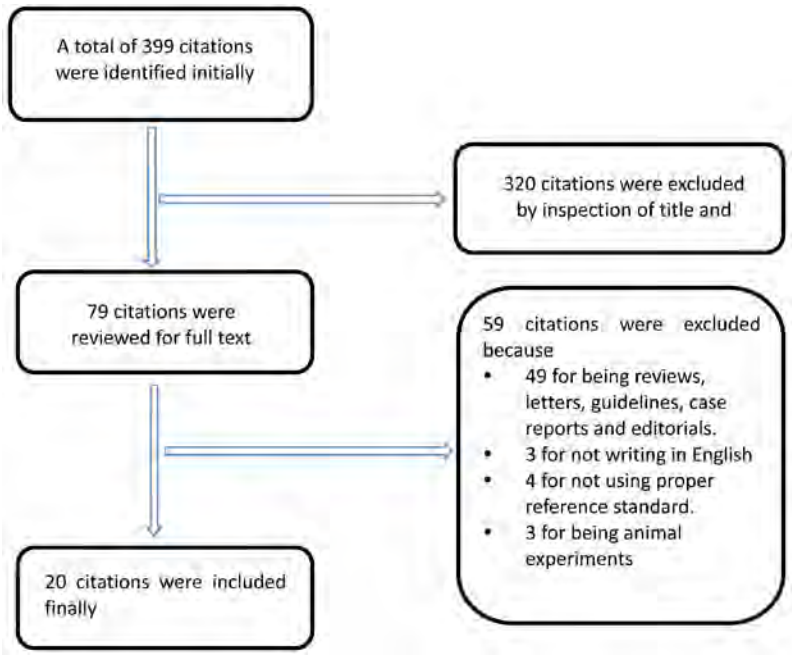


Figure 1. Flow chart of study selection.

Table 1. Characteristics of the studies included.

Study	Type of patients	Sample size	Setting	Type of device	Method for reference standard	Respiratory pattern	Index formula	reference standard	volume expansion
Barbier *et al.* 2004 [12]	adults	20	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8.5 ± 1.5 mL/kg; PEEP = 4 ± 2 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CI > 15%	7 ml/kg plasma
Feissel *et al.* 2004 [13]	adults	39	ICU	Not mention	Echocardiography	Mechanical ventilation (TV = 8 - 10 mL/kg)	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	CO > 15%	8 ml/kg 6% hydroxyethlstarch
Moretti and Pizzi 2010 [14]	adults	29	ICU	Esaote MyLab 30 CV	Transpulmonary, thermodilution	Mechanical ventilation (TV = 8 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CI > 15%	7 ml/kg 6% hydroxyethlstarch
Deok *et al.* 2010 [15]	children	21	Pediatrics	Acuson Cypress Diagnostic Ultrasound System	Echocardiography	Mechanical ventilation (TV = 10 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	SV > 15%	10 ml/kg 6% hydroxyethlstarch
Machare-Delgado 2011 [16]	adults	25	ICU	M-turbo, Sonosite, Bothell	Echocardiography	Mechanical ventilation (TV = 8.6 mL/kg)	(IVCmax − IVCmin)/IVCmin	SVI > 10%	500 ml saline
Corl *et al.* 2012 [17]	adults	26	ED	M-turbo, Sonosite, Bothell	ICG	Spontaneously breathing	(IVCmax − IVCmin)/IVCmax	CI > 10%	passive leg raise
Muller *et al.* 2012 [18]	adults	40	ICU	Vivid S6 machine, GE	Echocardiography	Spontaneously breathing	(IVCmax − IVCmin)/IVCmax	VTI > 15%	500 ml 6% hydroxyethlstarch
Brun *et al.* 2013 [19]	adults	23	Anesthesiology and obstetrics	Philips	Echocardiography	spontaneously breathing	(IVCmax − IVCmin)/[(IVCmax + IVCmin)/2]	SVI > 15%	500 ml normal saline

Continued

Byon HJ 2013 [20]	children	33	Operation room	Vivid 7, Pro, GE	Echocardiography	Mechanical ventilation (PEEP = 0 cm H_2O)	(IVCmax – IVCmin)/[(IVCmax + IVCmin)/2]	SVI > 10%	10 ml/kg hydroxyethlstarch
Baker *et al.* 2013 [21]	adults	25	ICU	Philips	Echocardiography	Mechanical ventilation (TV 6 - 8 mL/kg; PEEP 5 - 8 cmH2O	(IVCmax – IVCmin)/IVCmin	SV > 15%	500 ml colloid
Lanspa *et al.* 2013 [22]	adults	14	ICU	Philips	Echocardiography	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	CI > 15%	10 ml/kg crystalloid
Charbonneau *et al.* 2014 [23]	adults	44	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 6.4 - 11.0 mL/kg; PEEP = 5- 12 cm H_2O)	(IVCmax – IVCmin)/IVCmin	CI > 15%	7 ml/kg 6% hydroxyethlstarch
de Valk *et al.* 2014 [24]	adults	45	ED	Zonare, Mountain View	Systolic blood pressure	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	SBP > 10 mmHg	500ml 0.9% NaCl
Sobczyk *et al.* 2015 [25]	adults	50	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 4.5 cm H_2O	(IVCmax – IVCmin)/IVCmin; (IVCmax – IVCmin)/IVCmax	CO > 15%	2625 ± 778 mL within the first 6 hours
Lujan,varas *et al.* 2015 [26]	adults	15	ICU	Not mention	Picco, Vigileo, Swan-Ganz	Mechanical ventilation (PEEP11.4 ± 3.74)	(IVCmax – IVCmin)/IVCmin	CO > 15%	passive leg raise
Airapetian *et al.* 2015 [27]	adults	59	ICU	Philips	Echocardiography	Spontaneously breathing	(IVCmax – IVCmin)/IVCmax	CO > 10%	500 ml saline
Weber *et al.* 2015 [28]	children	31	PICU	Vivid S6; GE	Echocardiography	Mechanical ventilation (TV = 7.9 ± 3.8 mL/kg; PEEP = 6.8 ± 1.8 cm H_2O)	(IVCmax – IVCmin)/IVCmin	SVI > 10%	10 ml/kg 6% hydroxyethlstarch

Continued

Achar *et al.* 2016 [29]	children	42	Operation room	Vivid e; GE	Echocardiography	Mechanical ventilation (TV = 10 mL/kg; PEEP = 0 cm H_2O)	(IVCmax − IVCmin)/IVCmin	SVI > 15%	10 ml/kg 1% dextrose Ringer's lactate
Sobczyk *et al.* 2016 [30]	adults	35	ICU	Philips	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 4.5 cm H_2O)	(IVCmax − IVCmin)/IVCmin	CO > 15%	250 ml saline
de Oliveira *et al.*2016 [31]	adults	20	ICU	Samsung Medison	Echocardiography	Mechanical ventilation (TV = 8 mL/kg; PEEP = 5 - 6 cm H_2O)	(IVCmax − IVCmin)/IVCmin	VTI > 15%	500 crystalloid

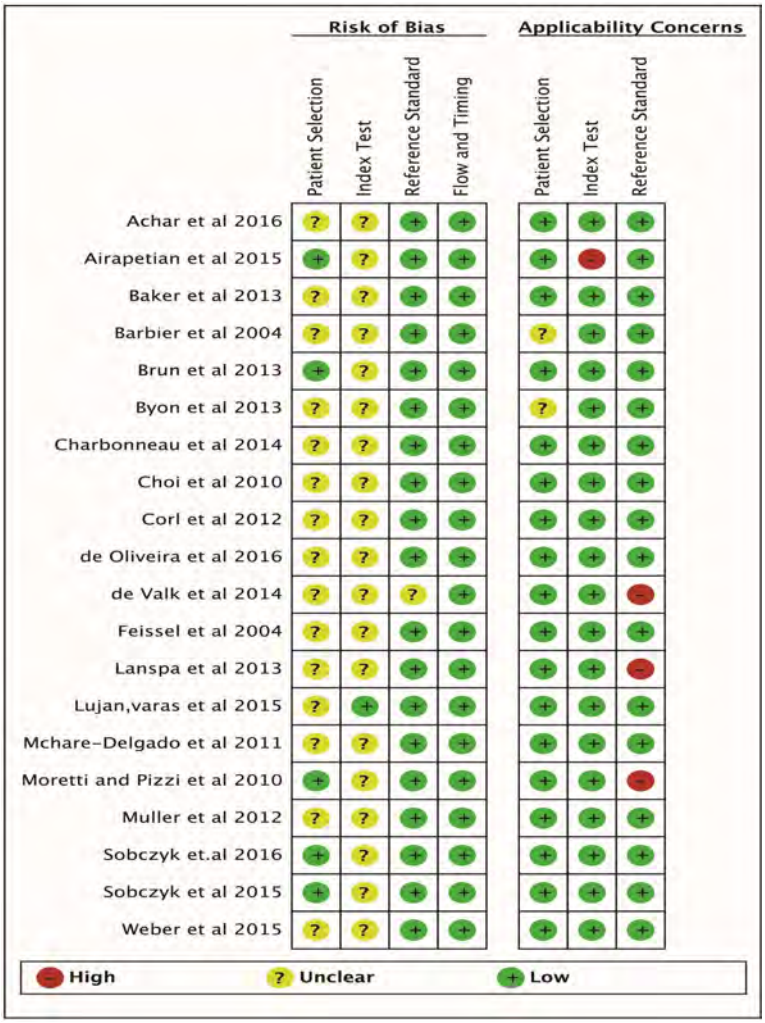
IVCmax and IVCmin = maximum and minimum diameter of inferior vena cava during a complete respiratory cycle; CI = cardiac index; CO = cardiac output; VTI = velocity-time index; SV = stroke volume; SVI = stroke volume index; SBP = systolic blood pressure; TV = tidal volume.

small, ranging from 14 to 50 patients. A total of 635 patients were included. 16 studies [12] [13] [14] [16] [17] [18] [19] [21]-[27] [30] [31] enrolled adults, and 4 studies [15] [20] [28] [29] enrolled pediatric patients. 14 studies [12] [13] [14] [15] [16] [20] [21] [23] [25] [26] [28] [29] [30] [31] enrolled patients on mechanical ventilation, and 6 studies [17] [18] [19] [22] [24] [27] enrolled spontaneously breathing patients. The formulas for the calculation of ΔIVC during the respiratory cycle were different. (IVCmax − IVCmin)/IVCmin was used in 11 studies [12] [14] [16] [21] [23] [25] [26] [28] [29] [30] [31], (IVCmax − IVCmin)/IVCmax was used in 5studies [17] [18] [22] [24] [27] and (IVCmax − IVCmin)/[(IVCmax + IVCmin)/2] was used in 4 studies [13] [15] [19] [20]. Interestingly, the 11 studies using the formula (IVCmax − IVCmin)/IVCmin allfocused on mechanically ventilatedpatients, and the 5 studies using the formula (IVCmax − IVCmin)/IVCmaxall focused on spontaneously breathing patients. In the 4 studies using (IVCmax − IVCmin)/[(IVCmax + IVCmin)/2] as the formula, one study focused on spontaneously breathing patients, while the other three studies focused on mechanically ventilated patients. With respect to reference standard, fluid responsiveness was defined as an increase in SV, CO or surrogate by more than 15% in 14 studies [12] [13] [14] [15] [18] [19] [21] [22] [23] [25] [26] [29] [30] [31], 10% in 5 studies [16] [17] [20] [27] [28], and increase in SBP by more than 10 mmHg in 1 study [24]. 16 studies [12] [13] [15] [16] [18]-[23] [25]-[31] used echocardiography to measured SV, CO or surrogate, 2 studies [14] [26] used transpulmonary thermodilution technique to measure CO, 1 study [17] used bioimpedance to measure cardiac index (CI) and the last study [24] used arterial catheter to measure SBP. VE was performed by

crystalloids in 8 studies [16] [19] [22] [24] [27] [29] [30] [31], by colloids in 10 studies [12] [13] [14] [15] [18] [20] [21] [23] [25] [28], passive leg raise in 2 studies [17] [26]. Quality assessment according to QUADAS-2 criteria is outlined in Figure 2.

3.2. Prediction of Fluid Responsiveness by ΔIVC

The diagnostic performance of ΔIVC in each study is showed in Table 2. The



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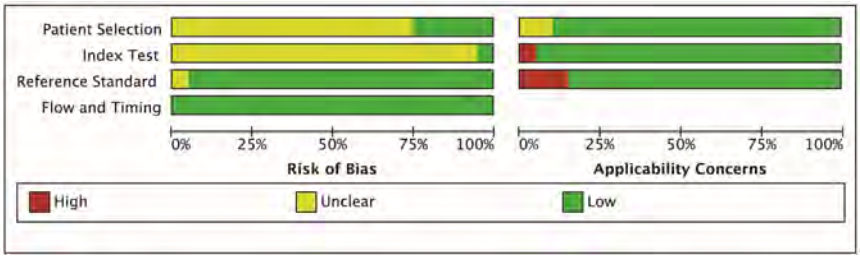

(b)

Figure 2. QUDAS-2 results and summary.

Table 2. Sensitivity and specificity of ΔIVC in predicting fluid responsiveness.

Study	TP	FP	FN	TN	Cutoff value	Sensitivity (%)	Specificity (%)	AUROC (95% CI)
Barbier *et al.* 2004	9	1	1	9	18%	90.00	90%	0.91 (0.84, 0.98)
Feissel *et al.* 2004	14	1	2	22	12%	-	-	-
Moretti and Pizzi 2010	12	0	5	12	16%	70.59%	100%	0.902 (0.733, 0.979)
Deok *et al.* 2010	-	-	-	-	-	-	-	0.85 (0.69, 1.00)
Machare-Delgado 2011	8	8	0	9	12%	100.00	53%	0.81 (0.64, 0.99)
Corl *et al.* 2012	-	-	-	-	-	-	-	0.46 (0.21, 0.71)
Muller *et al.* 2012	14	4	6	16	40%	70	80%	0.77 (0.60, 0.88)
Brun *et al.* 2013	-	-	-	-	-	-	-	0.57 (0.32, 0.82)
Byon HJ 2013	-	-	-	-	-	-	-	0.369 (0.156, 0.582)
Baker *et al.* 2013	-	-	-	-	-	-	-	0.46 (0.22 - 0.69)
Lanspa *et al.* 2013	5	3	0	6	15%	100	66.66%	0.83 (0.58 - 1.0)
Charbonneau *et al.* 2014	10	7	16	11	21%	38	61%	0.43 (0.25, 0.61)
de Valk *et al.* 2014	10	11	2	22	36.5	83	67%	0.741
Sobczyk *et al.* 2015	-	-	-	-	-	-	-	-
Lujan, varas *et al.* 2015	2	2	1	10	18%	-	-	-
Airapetian *et al.* 2015	9	1	20	29	42%	31	97%	0.62 ± 0.07 (0.49 - 0.74)
Weber *et al.* 2015	-	-	-	-	-	-	-	0.502 (0.29, 0.71)
Achar *et al.* 2016	22	2	2	16	23.5%	91	89%	0.94
Sobczyk *et al.* 2016	20	3	4	8	18%-	82.35%-	72.72%-	0.739
de Oliveira *et al.* 2016	6	0	3	11	16%	66.67	100%	0.84 ± 0.10 (0.63 - 1.0)

TP = true positive; FP = false positive; FN = false negative; TN = true negative; AUROC = area under the receiver operating characteristic curve; CI = confidence interval.

sensitivity and specificity was reported in 14 studies [12] [13] [14] [16] [18] [19] [22] [23] [24] [26] [27] [29] [30] [31]. The pooled sensitivity, specificity and DOR was 0.68 (0.62 - 0.75), 0.80 (0.75 - 0.85) and 14.2 (6.0 - 33.6), respectively. (**Table 2**, **Figure 3**). The area under the corresponding ROC curve was reported in 17 studies [12] [14]-[24] [27] [28] [29] [30] [31]. In 9 studies [12] [14] [15] [16] [18] [22] [24] [29] [31], the AUROC of ΔIVC were more than 0.7, and in the other 8 studies [17] [19] [20] [21] [23] [27] [28] [30], ΔIVC showed low diagnostic value. The pooled AUROC was 0.86 (0.78 - 0.93) (**Table 2**, **Figure 4**). The threshold of ΔIVC was reported in 13 studies [12] [13] [14] [16] [18] [22] [23] [24] [26] [27] [29] [30] [31], the values varied across studies, ranging from 12% to 42% (**Table 2**).

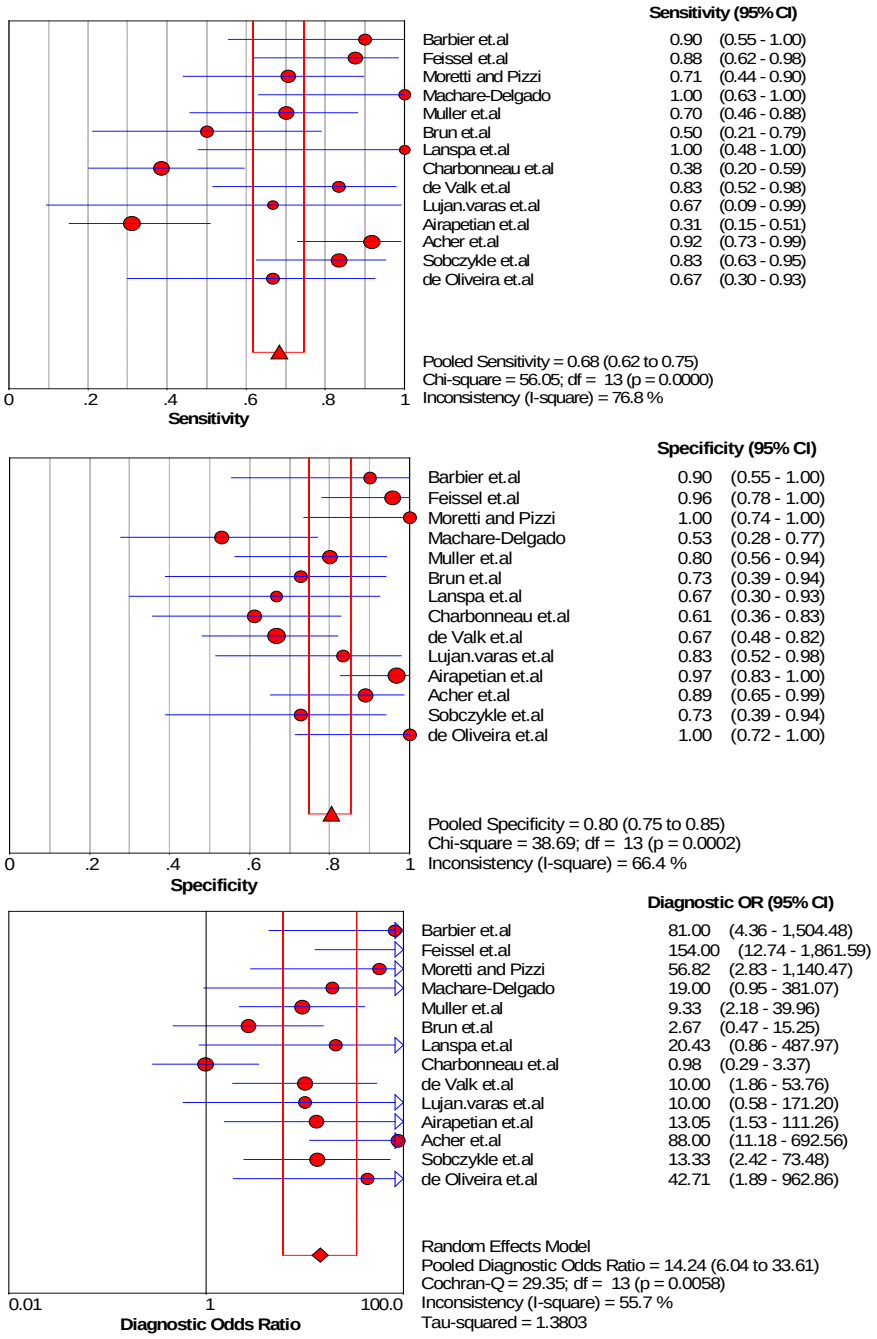

Figure 3. Pooled diagnostic accuracy of ΔIVC in whole studies.

3.3. Subgroup Analysis and Investigation of Heterogeneity

The Spearman correlation coefficient between sensitivity and specificity was 0.323 (p = 0.260), indicating no threshold effect. The heterogeneity Chi-squared was 56% for sensitivity and 39% for specificity. The I^2 statistics was 77% for sensitivity, 66% for specificity.

Meta-regression shows none of the covariates included were the significant source of heterogeneity. However, the comparison between studies with mechanical ventilation versus studies with spontaneously breathing, and between

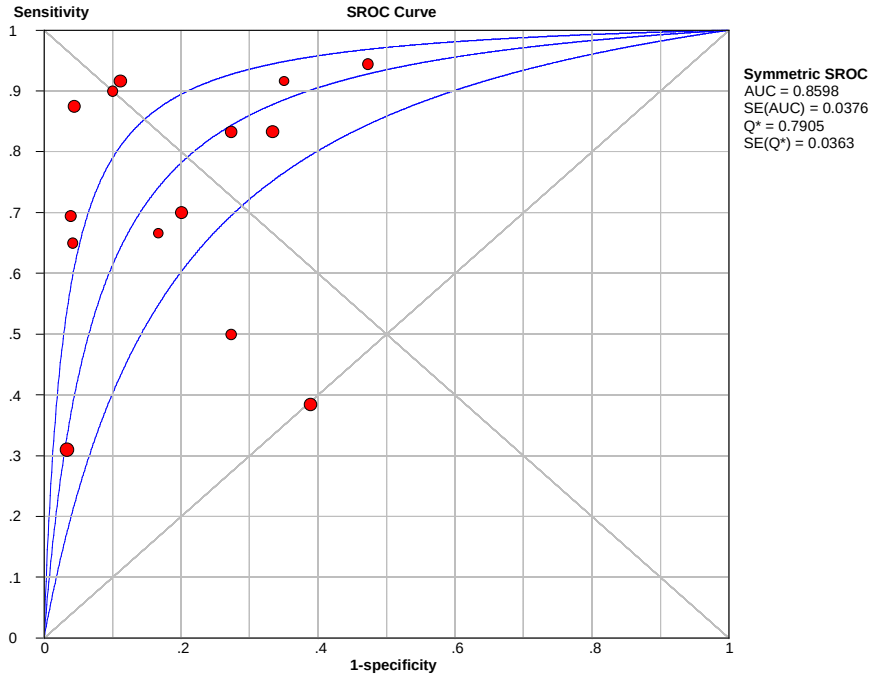

Figure 4. Summary receiver operating characteristics curve of ΔIVC in whole studies.

studies with different devices and formulas for the calculation of ΔIVC had influence on sensitivity and specificity. Diagnostically, ΔIVC performed better in patients on mechanical ventilation than in spontaneously breathing patients with higher sensitivity (0.75 vs.0.56), specificity (0.82 vs. 0.78), DOR (22.9 vs. 7.9), and AUROC (0.9 vs.0.8) (**Table 3**). In addition, 9 studies [12] [13] [14] [16] [23] [26] [29] [30] [31] with mechanical ventilation reported the threshold ranging from 12% to 23.5%, the average was 17% ± 4%; the average of the other 4 studies [18] [22] [24] [27] with spontaneously breathing was 33% ± 12%.

4. Discussion

This meta-analysis including 20 studies with a combined total of 635 patients concluded that ICU staff must be cautious of using ΔIVC, which was not so excellent to predict fluid responsiveness with pooled sensitivity (0.68) and specificity (0.80).In patients on mechanical ventilation, ΔIVC could predict fluid responsiveness moderately with acceptable pooled sensitivity (0.75) and specificity (0.82). The pooled AUROC was 0.90 (0.80 - 0.99) and the average of threshold was ΔIVC ≥ 17% ± 4%. However, in spontaneously breathing patients, ΔIVC predict fluid responsiveness with poor sensitivity (0.56) and acceptable specificity (0.78).

Point-of-care ultrasonography is a reliable monitoring technique and is becoming increasingly popular in the ICU. The IVC diameter is easily examined from a subcostal view in a longitudinal section, varying during the respiratory cycle due to the changes in intrathoracic pressure during inspiration and expiration. This variation is expressed as the ΔIVC. Recent years, ΔVC has been developed to

Table 3. Pooled diagnostic accuracy of ΔIVC in whole and subgroup studies.

Setting	Total number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic odds ratio (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95%CI)	AUROC
Overall	14	0.68 (0.62 - 0.75)	0.80 (0.75 - 0.85)	14.2 (6.0 - 33.6)	3.3 (2.1 - 5.1)	0.34 (0.21 - 0.54)	0.86 (0.78 - 0.93)
Mechanical ventilation	9	0.75 (0.67 - 0.82)	0.82 (0.74 - 0.88)	22.9 (5.6 - 93.4)	4.3 (2.0 - 9.4)	0.27 (0.13 - 0.54)	0.90 (0.80 - 0.99)
Spontaneous breathing	5	0.56 (0.45 - 0.68)	0.78 (0.70 - 0.86)	7.9 (3.5 - 18.1)	2.7 (1.8 - 4.0)	0.50 (0.29 - 0.86)	0.80 (0.71 - 0.89)

accurately predict fluid responsiveness in clinical practice. The consensus on circulatory shock and hemodynamic monitoring published by task force of the European Society of Intensive Care Medicine in 2014 recommended that ΔIVC as dynamic variables were available to predict fluid responsiveness [32].

To our knowledge, in 2014, Zhang and co-workers performed a systematic review and meta-analysis that included eight studies investigating the diagnostic performance of ΔIVC [9]. They concluded that ΔIVC is of great value in predicting fluid responsiveness, particularly in patients on mechanical ventilation compared to spontaneously breathing patients. However, since this meta-analysis, additional studies [19] [20] [21] [23] [25] [26] [27] [28] have been published, reporting ΔIVC would not be reliable in spontaneously breathing patients. In addition, G. Via *et al.* [33] have suggested ten situations where ΔIVC may fail to accurately predict fluid responsiveness. Furthermore, the threshold of ΔIVC varied widely, causing confusion of ICU staff to use it in clinical practice. Finally, the meta-analysis of Zhang *et al.* included only one study [18] investigating spontaneously breathing patients and four studies [12] [13] [14] [16] on mechanical ventilation with complete data. All these arguments justified an updated meta-analysis.

Our meta-analysis is inconsistent with the meta-analysis performed by Zhang *et al.* and concluded that ICU staff must be cautious of using ΔIVC to test fluid responsiveness. Based on the results from a large number of patients, we found that ΔIVC was not so excellent to predict fluid responsiveness with poor sensitivity (0.68) and acceptable specificity (0.80). The pooled AUROC was 0.86 but not close to each other. In addition, the threshold values for ΔIVC varied across studies, ranging from 12% to 42%, which reinforce our conclusion.

In subgroup analysis, our study indicated that in patients on mechanical ventilation, ΔIVC predict fluid responsiveness with acceptable pooled sensitivity (0.75) and specificity (0.82), which are less accurate than meta-analysis performed by Zhang *et al.*, however. This is likely due to high PEEP and/or low tidal volume invalidating the diagnostic performance of ΔIVC. High PEEP has been demonstrated to elevate right atrial pressure (RAP) and IVC pressure, while simultaneously reducing venous return, introducing an increase IVC size and false negative of ΔIVC [34]. Furthermore, the low tidal volumes less than 8 ml/kg will cause smaller variations in intrathoratic blood volume, resulting in smaller ΔIVC theoretically, irrespective of volume status. Charbonneau *et al.* [23] sug-

gested that ΔIVC predicted fluid responsiveness with low sensitivity (38%), and Baker *et al.* [21] demonstrated that ΔIVC was an inaccuracy predictor with low AUROC (0.46). The ventilation of these two studies was High PEEP > 5 cm H_2O and low tidal volumes < 8 ml/kg. However, these two studies [21] [23] were published after the meta-analysis performed by Zhang *et al.* In addition, our study indicated that in spontaneously breathing patients, ΔIVC predict fluid responsiveness with poor sensitivity (0.56) and acceptable specificity (0.78). The pooled AUROC was 0.80 (0.71 - 0.89). This is probably because of varying breath, meaning that the amplitude of intrathoracic pressure swings and size of tidal volumes are hard to quantify in spontaneously breathing patients. Study in healthy volunteers [35] shows deeper the breathing is, the larger diaphragmatic motion and ΔIVC are, regardless of volume status. This indicates that shallow breaths may minify ΔIVC and reduce its sensitivity, while inspiratory efforts may magnify ΔIVC and reduce its specificity [18]. Even if in patients on ventilation, ΔIVC is not a valid measure when patients made an inspiratory effort [36].

An important point that must be paid more attention to is the formula of calculation of ΔIVC. ΔIVC is usually expressed as the difference between expiratory IVC diameter and inspiratory IVC diameter divided by the expiratory IVC diameter, multiplied by 100%. However, in spontaneous respiration or mechanical ventilation, the changes of IVC diameter are opposite because of opposite changes of intrathoracic pressure during inspiration. In patients on mechanical ventilation, ΔIVC is calculated by (IVCmax − IVCmin)/IVCmin defined as IVC distensibility index (ΔdIVC), while in spontaneously breathing patients, it is calculated by (IVCmax − IVCmin)/IVCmax defined as IVC collapsibility index (ΔcIVC). In our meta-analysis, the best threshold of ΔIVC in patients on mechanical ventilation was ΔdIVC ≥ 17% ± 4%, compared to ΔcIVC ≥ 33% ± 12% in spontaneously breathing patients. Nowadays, the clinical use of ΔIVC is in chaos regardless of its physiology, leading to misjudgment, which need to be more accurate define and recognition.

There are some limitations that should be noted for interpreting the results. First, the heterogeneity of the included studies existed with respect to patient population, respiratory pattern, calculation formula, definition of index test and fluid responsiveness. Nevertheless, no threshold effect was detected. Furthermore, both the subgroup analyses and meta-regression were opposed to the influence of heterogeneity on the results. Second, although we performed subgroup analysis, the number of studies and sample size in each subgroup was small, the conclusion needs to be validated in future trials. Third, we did not include studies not in English, non-full-text and unpublished studies, which may increase the risk of reporting bias.

5. Conclusion

In conclusion, our meta-analysis indicated that ΔIVC is not an excellent predictor of fluid responsiveness in patients with acute circulatory failure. The pre-

dicting ability of ΔIVC was moderate in patients on mechanical ventilation, while it was poor in spontaneously breathing patients. Thus, intensivist must be cautious of using ΔIVC.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Electron Microscopic Investigation of Anterior Lens Capsule and Epithelium in Patients with Diabetes Mellitus

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Abstract

Purpose: To evaluate the histopathologic alterations of organelles in the epithelium of the anterior lens capsule. **Methods:** The interventional study included 26 eyes; of which 11 had non-proliferative diabetic retinopathy (diabetic group) and cataract, and 15 had age-related cataract (control group). We investigated the anterior lens capsule in patients with diabetes mellitus by using electron microscopy and to compare it between diabetic eyes and healthy eyes. Anterior capsule samples were obtained by circular continuous capsulorhexis during phacoemulsification procedures. All the samples were fixed and conventionally processed for electron microscopy analysis. **Results:** Demographic characteristics of the diabetic group and the control group were similar ($p > 0.05$). In the diabetic group, electron dense cells with an apoptotic appearance were seen and these cells had an apoptotic nucleus and prominent mitochondrial crystalysis. In addition, there was dilatation of the endoplasmic reticulum cistern. In the control group, lens epithelial cells and all their elements had a normal pattern. Neither cells with an apoptotic appearance nor mitochondrial crystalysis was seen, but there was dilatation of the endoplasmic reticulum cistern. **Conclusions:** Diabetes mellitus can engender structural abnormalities of organelles in the epithelium of the anterior lens capsule including mitochondrial crystalysis, dilatation of the endoplasmic reticulum cistern and apoptotic dense nucleus. It can be suggested that diabetes mellitus affects organelles of anterior lens epithelium in eyes with cataracts, while it causes non-proliferative changes in the retina.

Keywords

Anterior Lens Epithelium, Cataract, Diabetes Mellitus, Endoplasmic

Reticulum, Mitochondria

1. Introduction

Diabetes mellitus (DM) is the most significant cause of blindness in the world. Diabetes-related reactions are responsible for structural and functional changes in the eyes, and these changes are suspected of contributing to development of long-term diabetic complications like cataracts, glaucoma and retinopathy if DM is not kept under control well [1] [2].

Cataracts are one of the complications of DM starting the earliest. How excess glucose initiates cataract development in patients with diabetes mellitus has not been explained yet. Many of the common factors including sorbitol formation associated with aldose reductase activity, oxidative stress, protein glycation and formation of advanced glycation end products (AGE) have been implicated in diabetic cataract development [3] [4] [5]. The structure of the normal lens is almost perfectly transparent, which is regulated by physical and chemical processes. Disruption of these processes in the lens capsule and the epithelium can result in lens opacification and cataract formation [6]. However, histopathologic alterations of organelles in the epithelium of the anterior lens capsule with diabetic eyes have not been studied previously. Therefore, we investigated transmission electron microscopic findings of the epithelium of the anterior lens capsule in patients with DM and compared them with those from age matched controls.

2. Patients and Methods

This clinical prospective interventional study was performed at University of HealthSciences-Ulucanlar EyeEducationandResearchHospital. The study protocol was approved by the ethics committee of the hospital and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients included in the study.

The study comprised a total of 26 eyes with cataracts, of which 11 belonged to patients with Type II DM consecutively presenting to hospital (Diabetic Group = DG) and 15 belonged to nondiabetic patients with age related cataract (Control Group = CG). The diabetic patients were outpatients at Retina Department of Hospital and they had non-proliferative diabetic retinopathy. In both groups, anterior lens capsules were obtained during elective cataract surgery. Exclusion criteria included trauma, uveitis, glaucoma, history of previous intraocular surgery and history of long-term systemic or ocular therapy and systemic diseases. Cataracts were in nuclear or cortical forms in all the eyes and the subjects with mature or white cataract morphology were excluded from the study.

Glycosylated hemoglobin (HbA1c) levels were determined. Diabetic patients with HbA1c > 10 were not included in the study and DG only included type II-diabetic patients. All the patients were examined by an internal physician be-

fore surgery and non-diabetic patients with normal basal glycaemia were included in the study. None of the participants in the control group had ocular diseases except for senile cataracts.

All the cases underwent a comprehensive ophthalmic examination including best corrected visual acuity using the Snellen chart (20 feet), intraocular pressure measurement, slit lamp biomicroscopy and fundoscopy preoperatively. Results of blood tests including complete blood count, liver and renal function tests, fasting glucose levels and HbA1c levels were evaluated by an experienced internal specialist and the patients eligible for phacoemulsification surgery were determined.

All the cases underwent uncomplicated phacoemulsification surgery under local anesthesia. All the operations were performed by the same experienced surgeon (YOE). The anterior chamber was entered with a 2.8 mm keratome at the limbus. An ophthalmic viscosurgical device was injected into the anterior chamber. An anterior capsule flap was created with a cystotome and a circle of the central capsule with a diameter of 5 - 5.5 mm was carefully removed by continuous curvilinear capsulorhexis with forceps. The anterior capsule was fixed immediately. The lens capsule was not stained in all eyes.

The samples of the anterior lens capsule were kept in 2.5% glutaraldehyde for 24 hours for primary fixation. Then, these samples were washed with Sorenson's Phosphate Buffer solution (pH: 7.4) and post-fixed in 1% osmium tetroxide. After post-fixation, they were washed with the same buffer and dehydrated in increasing concentrations of alcohol series. Following dehydration, the tissues were washed with propylene oxide and embedded in epoxy resin embedding media. The semi-thin and ultrathin sections of the obtained tissue blocks were cut with an ultramicrotome (LKB Nova, Sweden). These semi-thin sections, which were 2 micrometers in thickness, were stained with methylene blue and examined under a light microscope (Nikon, Japan). Following this procedure, the tissue blocks were exposed to trimming and their ultrathin sections, which were about 60 nanometers in thickness, were taken by the same ultramicrotome. These ultra-thin sections were stained with uranyl acetate and lead citrate and examined under Jeol JEM 1200 EX (Japan) transmission electron microscope. The electron micrographs of the specimens were taken by the same microscope. Anterior lens capsule wrinkles were not observed during the preparation of the tissues.

Mann-Whitney U test and One-sample Chi-square test were used to compare the demographics characteristics. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows (SPSS, version 10.0, Inc., Chicago, IL, USA).

3. Results

The study included 26 eyes of 26 patients, of whom 11 formed the diabetic group (DG) and the remaining 15 formed the control group (CG). DG consisted of 5 males (45.5%) and 6 females (54.5%) and the mean age of this group was 67.18 ±

6.38 years. CG included 7 males (46.7%) and 8 females (53.3%) with a mean age of 65.38 ± 7.25 years. HbA1c levels were between 5.9 and 10 in DG. There were no significant differences in age and gender between CG and DG ($p > 0.05$).

Electron microscopic examination of the anterior lens capsules revealed significant ultrastructural changes in DG when compared to CG. In DG, electron dense cells with an apoptotic appearance were seen and these cells had an apoptotic nucleus and prominent mitochondrial crystalysis. Also, there was dilatation in the endoplasmic reticulum cisterns (Figure 1 and Figure 2). In CG, lens epithelial cells and all their elements had a normal pattern. Neither cells with apoptotic appearance nor mitochondrial crystalysis was observed, but there was dilatation in the endoplasmic reticulum cistern (Figure 3 and Figure 4).

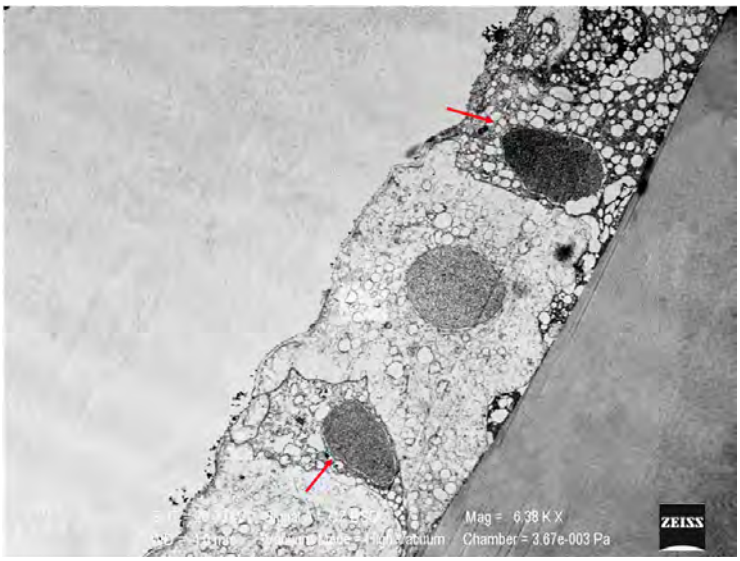

Figure 1. The appearance of apoptotic cells (red arrow) in DG.

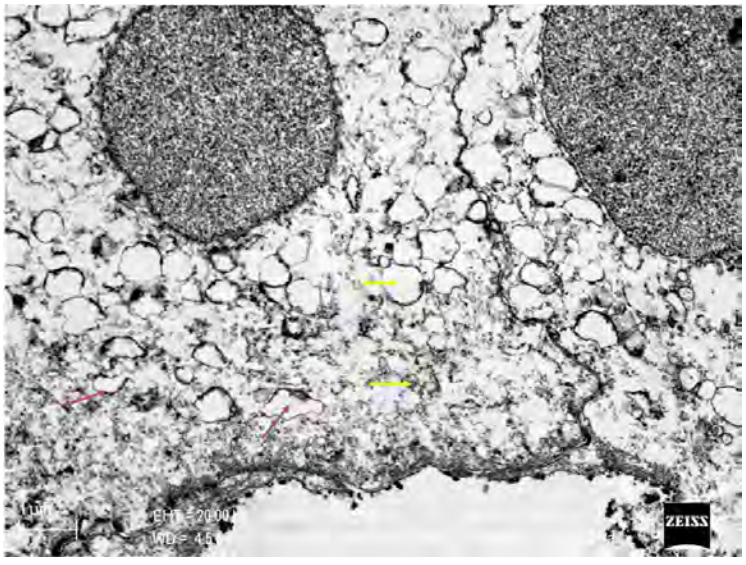

Figure 2. The dilatation of endoplasmic reticulum cistern (red arrow) and mitochondrial crystalysis (yellow arrow) in DG.

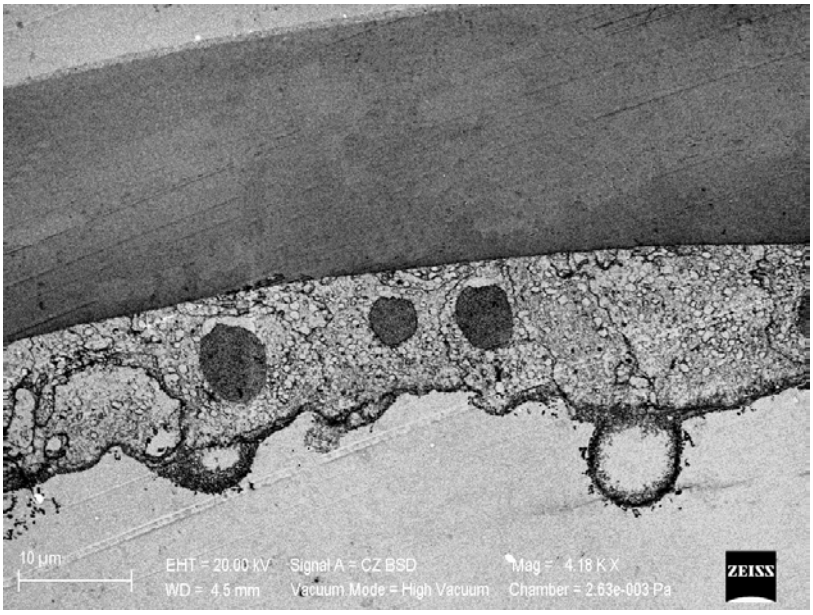

Figure 3. The normal epithelial cell in CG.

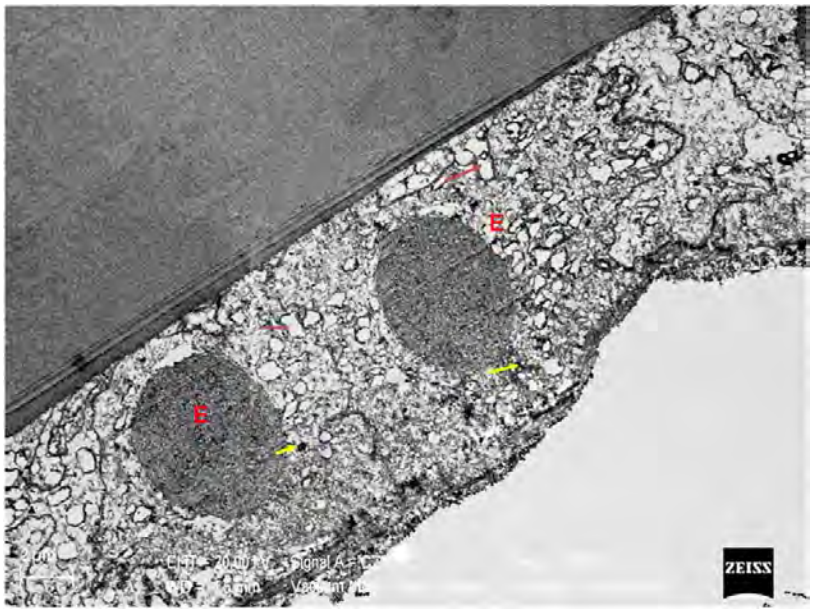

Figure 4. The normal appearance of epithelial cell and mitochondria (yellow arrow) and the dilatation of endoplasmic reticulum cistern (red arrow) in CG.

4. Discussion

Histologically, the structure of the lens comprises the lens capsule, the lens epithelium and the lens fiber [7] [8] [9] [10]. A modified transparent basement membrane secreted by the lens epithelial cells, the lens capsule is the thickest basement membrane having a specific structure and functions in the human body. The lens epithelium exhibits a characteristic epithelial morphology. Anterior lens epithelial cells are flattened cuboidal hexagonal in shape, are tightly packed in a single layer with very little intercellular space and contain a round

nucleus with a few apically distributed organelles, *i.e.* ribosomes, polysomes, smooth and rough endoplasmic reticulum (ER), and Golgi bodies. These cells have small mitochondria with irregular cristae. Each mitochondrion is surrounded by a smooth outer membrane and a folded inner membrane. The cristae, the folds of the inner membrane, considerably increase the surface area of the inner membrane and the surface area for ATP synthesis and reactions related to electron transport, Krebs citric acid cycle, and oxidative phosphorylation. Histologically, ER is made up of interconnected tubules and vesicles, the lumens of which are called the cistern, and it is the main site of protein synthesis [11] [12].

The lens capsule and the lens epithelium act as a regulating barrier between the aqueous humor and the lens fibers. Also, they allow for passive exchanging of metabolic substrates, expelling of wastes and selectively filtering molecules based on size and charge. They play a crucial role in preservation of lens transparency. Any factor which disturbs the transport processes, morphology or biochemistry of the lens capsule and the epithelium would lead to cataract formation [6] [13].

The present study was directed towards investigating transmission electron microscopic findings of organelles in the anterior lens capsule epithelium with DM and comparing them with those from age matched controls. All the diabetic anterior capsules in this study showed significant ultrastructural changes. To the best our knowledge, this is the first study to evaluate histopathological alterations in organelles of the anterior lens capsule epithelium of diabetic cataracts.

Cataracts are considered a major cause of visual impairment in patients with DM [14]. However, the exact pathogenesis of diabetic cataract development is completely unknown. Several factors including oxidative stress and generation of reactive oxygen species (ROS), aldose reductase and sorbitol pathway hyperactivity, and protein glycation and formation of AGEs have been held responsible for the development of diabetic cataracts in recent studies [3] [4] [5].

Until today, aldose reductase and sorbitol pathway hyperactivity have been reported in many studies to be associated with diabetic cataracts and it has been shown that increased intracellular sorbitol leads to localized osmotic stress. It is also known that intracellular accumulation of sorbitol and AGEs in the human lens leads to osmotic stress and hydropic degeneration of lens fibers. Increased osmotic stress initiates an apoptotic process in epithelial cells contributing to the cataract formation [3] [4] [5] [15]. Furthermore, aldose reductase and sorbitol pathway hyperactivity have been proposed to initiate oxidative stress and generation of ROS [16]. Moreover, it has been reported in many studies that chronic hyperglycemia may cause oxidative stress and formation of ROS [15]. Hyperglycemia related to mitochondrial dysfunction is the basic source of formation of oxidative stress specimens [17]. Additionally, stress of ER resulting from osmotic stress is another source of oxidative specimens [15] [18]. It can be estimated that mitochondrial dysfunction and ER stress in lens epithelial cell accelerate

lens opacification [14]. In addition, formation of AGEs through non-enzymatic glucose-protein reactions has been implicated in excessive glucose levels in DM. Normal accumulation of AGEs has also been observed in normal aging process [19].

Adults who have type 2 diabetes display cortical and/or posterior subcapsular opacities, which are often accompanied by nuclear sclerosis and which resemble typical senile cataracts of nondiabetics. Despite their morphological similarities, lenses with cataracts in diabetics have lower epithelial cell densities than those in healthy individuals [20] [21] [22]. The capsule and the epithelium of eyes with cataracts have morphological features, typical of aging cells such as altered hexagonal cellular arrays, and changes in the endoplasmic reticulum, the Golgi apparatus and the mitochondria [23].

In the present study, epithelial cells in abnormal lens with an apoptotic nucleus with prominent mitochondrial crystalysis were observed in the anterior capsules of the diabetic patients. It can be suggested that these ultrastructural changes may be caused by intracellular accumulation of sorbitol and AGEs and osmotic stress and associated with over expression of intrinsic mitochondrial apoptotic pathways in the lens capsules of these patients.

It has been noted in the literature that osmotic stress creates stress in the ER in diabetic patients [24] [25]. The stress in the ER initiates a series of protective signal transduction pathways from ER to the cytoplasm and nucleus, known collectively as the unfolded-protein response (UPR) [12]. The amount of unfolded protein can be monitored in the ER lumen. When it is higher than a certain threshold, ER sensors activate a signal transduction pathway. The responses activated by this pathway are referred to the UPR. Several cellular insults impair protein folding and lead to deposition of unfolded protein in the ER lumen. If there is not an adequate UPR adaptive response to repair the protein folding defect, apoptotic death of the cells starts. Furthermore, apoptosis is activated through cell death pathways which include multiple caspases and the release of produced reactive oxygen species and these outcomes may also lead to a UPR response [12] [24] [25]. It can be suggested that accumulation of UPR might have led to dilatation of ER cisterns in anterior lens capsules of the patients with DM in the current study. Additionally, the formation of reactive oxygen species and age-related AGE products might have caused retention of UPR and dilatation of ER cisterna in the control group.

The limitations of this study are that the study sample was small and only included non-proliferative diabetic eyes with type II DM. For this reason, the findings cannot be generalized to all diabetic patients.

In conclusion, DM can lead to some significant changes including apoptotic dense nucleus, prominent mitochondrial crystalysis and dilated endoplasmic reticulum in the anterior lens epithelium of eyes with non-proliferative stage. It can be suggested that diabetes mellitus may affect organelles of anterior lens epithelium in eyes with cataracts, while it causes non-proliferative changes in the

retina. It can be expected that understanding of the complex mechanisms would lead to discovery and development of innovative therapeutic intervention strategies for diabetic patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Relationship of Pre-Existing Maternal/Caregiver Acute Respiratory Infection in the Pattern and Risk of Acute Respiratory Infection among Infants in Rivers State, Nigeria

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Abstract

History of upper respiratory tract infection in the mother or siblings was associated with higher risk of acute lower respiratory tract infection in cases. Most upper respiratory tract infections were caused by viral pathogens and likely to occur in many members of the family. The study aimed to determine the existence and pattern of relationship between risk of acute respiratory infection (ARI) among infants and exposure to pre-existing maternal/caregiver acute respiratory tract infection. The study was designed as a community-based Nested case-control study of 1100 infants randomly selected from 12 communities out of 6 Local Government Areas of the 3 senatorial districts of Rivers State. A multistage random sampling technique was used in selecting the subjects up to the community level. Descriptive method was used to represent the characteristics of the subjects and the differences in ARI between exposed and unexposed infants were tested in a bivariate logistics regression at 5% level of significance. Odds ratio (OR) was used to interpret the size effect measures of ARI on exposure to pre-existing maternal/caregiver ARI differences. A total of 275 Cases of ARI and 825 controls were included in the study. Among exposed infants (N = 104), ARI cases were found to be higher n = 80 (76.9%) than in control n = 24 (23.1%). Whereas, among unexposed infants N = 991, ARI cases were found to be lower n = 195 (19.7%) than in control n = 796 (80.3%). For the exposed infants, the odds for ARI were 13.5 times significantly higher compared to those of their unexposed counterparts (OR-Unadjusted = 13.52, ($p < 0.0001$, 95% CI = 0.047 - 0.121)).

The findings will widen the horizon in the etiological consideration of ARI among infants vis-à-vis exposure potential to pre-existing maternal/caregiver ARI via nursing care. Therefore, community-based sensitization programme on barrier nursing care techniques and personal hygiene practices should be on focus.

Keywords

Acute-Respiratory-Infection, Pattern, Risk-Factor, Maternal/Caregiver, Pre-Existing, Barrier-Nursing

1. Introduction

Acute respiratory infection (ARI) is defined as an infection characterized by presence of cough with or without fever for less than two weeks [1]. According to [2], ARI is defined as "an episode of acute symptoms and signs resulting from infection of any part of respiratory tract or related structure, including nose, throat, larynx, trachea, bronchi, bronchioles, lungs, para-nasal and middle ear. A new episode is one occurring in an individual who had been free of symptoms for at least 48 hours".

Pattern in view of epidemiology refers to variation in the manifestation characteristics of health-related events in persons [3], while risk factor in our present discuss refers to factor related to the host and or environment that increases the chances of morbidity (ARI) in infants.

The study from [4], reported that mothers with pneumonia were more likely to deliver prematurely, and have infants of lower birth weight. It is quite possible that the cascade of mediators released by the active host inflammatory response to infection exerts distant effects on the uterus, leading to a high rate of preterm labor during the course of pneumonia. Literatures had equally reported low birth weight among infants as risk factor for ARI in young children; this implies that exposure to pre-existing maternal pneumonia may increase the potential for ARI in infancy from an epidemiological point of view, whose principle and theoretical concepts form the basis for this research work. Our focus in this study was infant exposure to maternal/caregiver respiratory secretions and or droplets by way of nursing care or proximity.

It was reported that an important epidemiologic feature of virtually all influenza pandemics and seasonal epidemics of any degree of severity is the existence of specific groups of people at elevated risk for severe complications and death, including the very young, the very old and patients with underlying chronic respiratory and cardiovascular conditions and pregnant women and their fetuses they carry [5] [6]. Reports had also shown that about 90% of causative agents of acute respiratory infections are viral agents [7] [8] [9] [10] [11], in which the influenza virus is inclusive and known to be highly contagious. This implied that from disease occurrence point of view, such epidemiologic feature

may be equally observed in all acute respiratory infections.

Further report showed that maternal influenza vaccination had been demonstrated to reduce influenza associated hospitalizations in infants under six (6) months old by 45% - 48% [12].

The study by [13], showed that history of upper respiratory tract infection in the mother or siblings was associated with higher risk of acute lower respiratory tract infection in cases. Most of upper respiratory tract infections were caused by viral pathogens and viral infections are highly contagious and likely to occur in many members of the family. Viral upper respiratory tract infection may predispose a child to acute lower respiratory tract infection [14].

It is therefore auspicious to determine the relationship of pre-existing maternal/caregiver ARI in the pattern and risk of acute respiratory infection among infants in view of this study which may have direct innovative prevention and nursing care measures at household level that will complement efforts directed at case management.

1.1. Aim of the Study

The study aimed to determine the existence and pattern of relationship between risk of ARI among infants and exposure to pre-existing maternal/caregiver acute respiratory tract infection.

1.2. Research Hypothesis

Null Hypothesis H_0—There is no relationship between pattern and risk of ARI and exposure to pre-existing maternal/caregiver acute respiratory tract infection/diseases among infants in Rivers State, Nigeria.

Alternative Hypothesis H_1—There is relationship between pattern and risk of ARI and exposure to pre-existing maternal/caregiver acute respiratory tract infection/diseases among infants in Rivers State, Nigeria.

2. Materials and Methods

2.1. Research Design

The design used for this study was community-based prospective-retrospective (Nested) case-control method, aimed at determination of the pattern and risk of ARI among infants in relation to pre-existing maternal/caregiver ARI in the study areas.

The inclusion criteria for cases were children not up to 12 months of age in the study areas with at least any two of the signs and symptoms of cough, running nose or fever less than three (3) days duration among others within two (2) weeks of enrollment/interview. While the inclusion criteria for controls were children not up to 12 months of age in the study areas without such signs and symptoms within two (2) weeks of enrollment/interview.

The exclusion criteria were removal of any case or control with difficulty in extracting complete information required for the study. See **Figure 1** for the schematic illustration of the design concept.

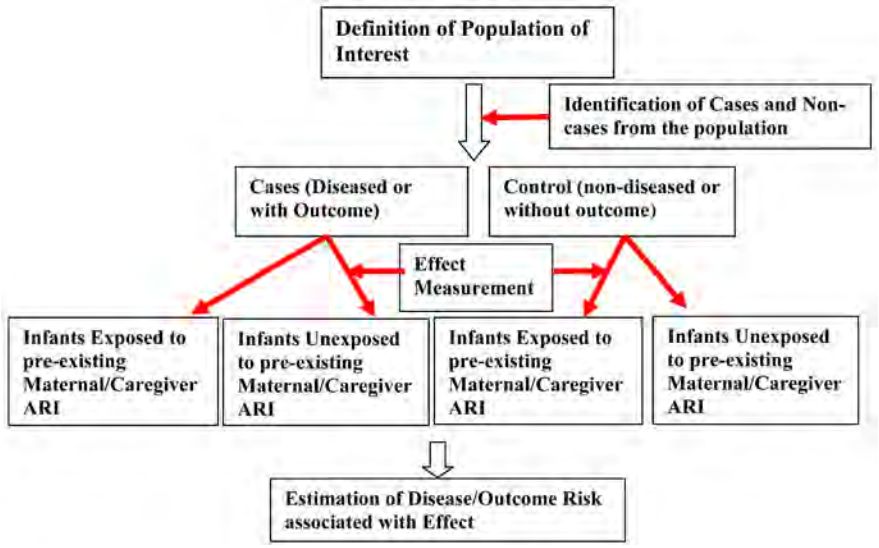

Figure 1. Schematic diagram of case-control study (observational study). Adapted from http://www.drcath.net/toolkit/casecontrol.html.

2.2. Area of Study

The study was carried out in both rural and urban settings, covering 12 communities in 6 Local Government Areas (LGAs), out of 23 LGAs in the 3 senatorial districts in Rivers State, Nigeria. Rivers State, with coordinates, latitudes 4˚51'29.0761" and 4˚51.4846'N, longitude 6˚55'15.2886" and 6˚55.2548'E, [15], is one of the 36 states in Nigeria, with Port Harcourt as the State capital. It occupies an area of about 37,000 square kilometers and bounded in the north by Imo and Abia States; in the south by the Atlantic Ocean; to the east by Akwa Ibom State and to the west by Bayelsa and Delta States.

The 12 communities, randomly selected as the points of sample include; Akinima and Okarki in Ahoada West LGA, Buguma City and Krakrama in Asari-Toru LGA, in Rivers West Senatorial District; Okehi and Chokocho in Etche LGA, Rumuwoji and Town city slum areas in Port Harcourt City LGA, in Rivers East Senatorial District; Oyigbo and Okoloma in Oyigbo LGA, Botem/Genebue-e and Nonwa in Tai LGA, in Rivers South East Senatorial District.

2.3. Study Population

The population used in this study was children less than 1-year-old in 12 selected communities in 6 LGAs in the 3 senatorial districts of Rivers State. The population of Nigeria was estimated to be at about 167 million (2006 census report) and children under 1year of age constitute 4% (6.6 million) of the total population [16].

In developing countries, including Nigeria, 10% - 15% of all ARI may progress to disease of moderate to severe intensity, [2], giving an estimate figure of such intensity to 29,040 to 43,560 cases in Nigeria annually with geographical zones and urban/rural settings variation.

Determination of Sample Size

The sample size for this study was based on [17] formula.

$$\text{Sample size} = r + 1\ (p^*)\ (1 - p^*)\ (Z_\beta + Z_{\alpha/2})^2/(P_1 - P_2)^2 \quad (1)$$

where; r = Ratio of Control to Case, 1 for equal number of Case and Control, p^* = Average proportion exposed = Proportion of Exposed Cases + Proportion of Control Exposed/2, Z_β = Standard normal variant for power = for 80% power it is 0.84 and for 90% power value is 1.26, $Z_{\alpha/2}$ = Standard normal variant for level of significance = 1.96, $P_1 - P_2$ = Effect size or different proportion expected based on previous studies. P_1 is proportion in cases and P_2 is proportion in control.

Therefore, from Equation (1) and assuming power of study of 80% (0.84), expected proportion in case group and control group to be 0.35 and 0.20 respectively and substituting values we have;

$$\text{Sample size} = 1 + 1\ (0.275)\ (1 - 0.275)\ (0.84 + 1.96)^2/(0.35 - 0.20)^2 = 138.9$$
$$\approx 139 \text{ Cases and Control each gives a total of 278 at least.}$$

For a matching power of 1 - 3, the minimum sample size required for this study is;

$$139 \times 3 = 417 + 139 = 556 \text{ Cases and Controls.}$$

However, for a representative sample population for the study, the number was increased proportionally from the selected communities, giving 1100 infants which are greater than 3% of the prevalence value considering the lower ARI prevalence rate of 10%, [2] that may progress to moderate to severe cases.

2.4. Sample and Sampling Techniques

The sample was selected using multi-stage simple random sampling techniques from the LGAs up to the community level through division of each of the communities into convenient zones, followed by selection of a ward in each zone by simple random technique. Also, through simple random technique one area of each ward was selected and study carried out starting from number 1 house in an order, after its determination by simple random techniques till the required number of infants was found. The techniques for sampling, also include Stratified Sampling by way of grouping sample population into age and place of residence. In addition, simple random sampling was used in picking required caregivers/infants of the sample population. In the simple random sampling, balloting was used in choosing the caregivers/infants and the control group who took part in the study, in this manner; every infant/mother/caregiver of the population was given a chance of being selected.

A total of 1100 infants comprising 275 cases and 825 controls (1:3) were picked proportionally, among the communities based on proportional allocation factor of 6:4 (660:440) for urban and rural communities for both cases and control, reflecting the size of study population of the communities, and a proportional allocation factor of 1:4.5:4.5 (100:500:500) for the age group of <2 months, 2 months - 6 months and 7 months up to 12 months. **Table 1** gives the summary of the study population per sampling points/LGA.

Table 1. Summary of study population per sampling points/LGA.

Sampling Point/LGA	Study Population	
	Cases	Controls
Ahoada West	42	126
Asari-Toru	44	132
Etche	44	132
Oyigbo	44	132
Tai	44	132
Port Harcourt City	57	174
Total	**275**	**825**

2.5. Instrument for Data Collection

The instrument used for data collection was set of structured questionnaires. The items were based on demographic characteristics, knowledge and attitude of the target/study population as it had to do with exposure potentials to pre-existing maternal/caregiver ARI in the pattern and risk of ARI among infants. The questionnaire as developed was reviewed for content validity. Pilot-testing for understanding of items by target/study population was done, using 10 caregivers/infants who did not form part of the sample used for the study.

The questionnaires were personally administered on the mothers/caregivers of the randomly selected infants for relevant information, by the researcher with the help of recruited Community Health Practitioners after one-day training on the pattern of administration of the questionnaires and retrieved on the same day.

To collect data on ARI, mothers/caregivers were asked whether their child under one (1) year of age had been ill with at least any two (2) of the three (3) signs and symptoms; cough, running nose or fever less than three (3) days duration within the two (2) weeks of enrollment/interview. Those infants who suffered from such outcome attributes of ARI at any time during the two (2) weeks of interview were identified or defined as having ARI as cases.

Data from control group of the study was generated from matched study population to the cases of ARI from the same referent population using an uncontrollable variable (age), grouped as less than two (2) months, two (2) months - six (6) months, seven (7) months up to twelve (12) months that ensures as much as possible that the 5% chance of erroneously rejecting the null hypothesis is not increased when making comparism of study variable between cases and control groups of the study.

2.6. Methods and Techniques for Data Analysis

Data from responses were collated and presented in a tabular form with nominal scale, showing values for cases and non-cases (control) for the variable of study (exposure to pre-existing maternal/caregiver ARI). The entries were double

checked for possible error of recording. Statistical analysis was performed using SPSS, version 21.0, to test the hypothesis for result at 5% significant level and also to show distribution of difference in exposed and unexposed infants. Descriptive method was used to represent the characteristics of the subjects and the differences in ARI between exposed and unexposed infants to pre-existing maternal/caregiver ARI were tested in a bivariate logistics regression at 5% level of significance. Odds ratio (OR) was used to interpret the size effect measures of ARI from exposure to pre-existing maternal/caregiver ARI differences.

2.7. Ethical Approval

Ethical approval for the study was gotten from the University of Port Harcourt Teaching Hospital Ethical Committee and the Research Ethics Group of the Centre for Medical Research and Training, College of Health Sciences, University of Port Harcourt. The nature and purpose of the study and level of participation of the respondents (mothers/caregivers) and their infants were clearly explained and their informed consent sought before the interview. Participation in the study was voluntary even after providing consent.

3. Results

Table 2 showed patterns of ARI and exposure status to pre-existing maternal/caregiver ARI of the study population in rural communities (N = 440), with the indication that, for the exposed category N = 49; n = 40 (81.6%) of the cases came under this category, against n = 9 (18.4%) of the controls who were also classified in the same category as at the two weeks of the interview/enrollment for the study.

For the category of unexposed N = 391; n = 321 (82.1%) of the controls were unexposed and came under this category, against, n = 70 (17.9%) of the cases who were also unexposed to pre-existing maternal/caregiver ARI and so equally classified under this category.

However, none of the cases and control infants from the rural communities fell under the category of unknown/indeterminate.

In Table 3, that showed the patterns of ARI and exposure status to pre-existing maternal/caregiver ARI among the infants from urban communities (N = 660), in which for the exposed category N = 55; n = 40 (72.7%) of the cases were under

Table 2. Patterns of acute respiratory infection and exposure status to pre-existing maternal/caregiver ARI of Infants in rural communities.

Exposure Status	Total (N)	Cases (n)	%	Controls (n)	%
Exposed	49	40	81.6	9	18.4
Unexposed	391	70	17.9	321	82.1
Unknown/Indeterminate	0	0	0	0	100
Total	**440**	**110**	**25**	**330**	**75**

Table 3. Patterns of acute respiratory infection and exposure status to pre-existing maternal/caregiver ARI of infants in urban communities.

Exposure Status	Total (N)	Cases (n)	%	Control (n)	%
Exposed	55	40	72.7	15	27.3
Unexposed	600	125	20.8	475	79.2
Unknown/Indeterminate	5	0	0	5	100
Total	**660**	**165**	**25**	**495**	**75**

this category, against n = 15 (27.3%) of the controls who were equally classified in the category within the period of the study.

In the category of unexposed N = 600; n = 475 (79.2%) of the controls were unexposed, against n = 125 (20.8%) of the cases who were also not exposed.

While, for the category of unknown/indeterminate N = 5; n = 5 (100%) of the infants' control status of exposure were unable to be determined, against none for the cases.

The evidences shown in Table 2 and Table 3 gave clear indication of existence of patterns relationship between ARI among infants and exposure to pre-existing maternal/caregiver ARI in rural and urban communities with a statistical difference of 11.8% higher in occurrence in rural communities.

Table 4, showing patterns of ARI and exposure status to pre-existing maternal/caregiver ARI of the study population (N = 1100), wherein n = 275 were cases while n = 825 were controls, indicated that, for the exposed category, total (N = 104); n = 80 (76.9%) were cases of ARI, against n = 24 (23.1%) who were controls (non-cases of ARI) as at the two weeks of the interview/enrollment for the study.

For the category of unexposed, total (N = 991); n = 796 (80.3%) were controls, against, 195 (19.7%) who were cases. However, for the category of unknown/indeterminate, total (N = 5); n = 5 (100%) of the infants' control status of exposure were unable to be determined, against none for the cases.

Therefore, considering the evidence provided by the data in Table 4, the cases presented a pattern relationship between exposure to pre-existing maternal/caregiver ARI and acute respiratory infection among infants, in which the exposed infants had higher frequency of 76.9% in occurrence, compared to 19.7% of the cases who were unexposed. We can in this wise, infer that patterns relationship between ARI among infants and exposure to pre-existing maternal/caregiver ARI was observed to exist in this study, with a statistical difference in frequency of 57.2% in occurrence.

Table 5 showed data on relationships between pre-existing maternal/caregiver acute respiratory infection and acute respiratory infection among infants, wherein out of total; N = 104 infants exposed to pre-existing maternal/caregiver acute respiratory infection, n = 80 infants came down with signs and symptoms of acute respiratory infection as cases, while n = 24 infants were without signs and symptoms of acute respiratory infection as controls within the 2 weeks of interview/enrollment for the study.

Table 4. Patterns of acute respiratory infection and exposure status to pre-existing maternal/caregiver ARI of study population.

Exposure Status	Total (N)	Cases (n)	%	Control (n)	%
Exposed	104	80	76.9	24	23.1
Unexposed	991	195	19.7	796	80.3
Unknown/Indeterminate	5	0	0	5	100
Total	**1100**	**275**	**25**	**825**	**75**

Table 5. Relationships between pre-existing maternal/caregiver acute respiratory infection and acute respiratory infection among infants.

Pre-existing maternal/ caregiver ARI	Cases (n)	Control (n)	Total (N)
Exposed	80	24	104
Unexposed	195	796	991
Total (N)	**275**	**825**	**1095**

Ref. = Exposed; OR-Unadjusted = 13.52, ($p < 0.0001$, 95% CI = 0.047 - 0.121); Unexposed.

Similarly, out of total; N = 991 infants unexposed to pre-existing maternal/caregiver acute respiratory infection, n = 195 infants came down with signs and symptoms of acute respiratory infection as cases, against n = 796 infants without signs and symptoms of acute respiratory infection as non-cases (controls) within the 2 weeks of interview/enrollment for the study.

On subjection of the data as presented in Table 5 to bivariate logistic regression analysis for odds ratio (unadjusted) to indicate if any association exist between pre-existing maternal/caregiver acute respiratory infection and acute respiratory infection among infants, revealed significant relationship OR-Unadjusted = 13.52, ($p < 0.0001$, 95% CI = 0.047 - 0.121), meaning infants exposed to pre-existing maternal/caregiver acute respiratory infections were more than 13 times at risk (OR = 13.5) of contracting ARI than infants without exposure to pre-existing maternal/caregiver acute respiratory infection.

4. Discussion

A relationship between pattern and risk of acute respiratory infection among infants and exposure to pre-existing maternal/caregiver acute respiratory infection, was observed in this study, noting that infants exposed to pre-existing maternal/caregiver acute respiratory infections are more than 13 times (OR = 13.5) at risk of contracting acute respiratory infection than their unexposed infants by bivariate logistic regression analysis. Also, statistical difference in patterns of ARI among infants and exposure status to pre-existing maternal/caregiver ARI between rura land urban communities was found to be 11.8% higher in occurrence in rural communities.

This finding corroborates with existing body of knowledge as reported in the studies by [12] [13]. This may provide explanation that, the influence of proxim-

ity and or close contact to source of infection, more so viral agents that are transmissible by airborne route to portal of entry into the body system is strategic in disease occurrence.

Nevertheless, the period of infancy in humans is influenced by several factors that regulate the susceptibility potential to respiratory tract infections among which are the immune factor; associated with immunosuppressed/hypo-responsiveness, lack of previous exposure/immune memory, reduced innate immune response and reduced adaptive immune response; viral factors; influencing inhibition of type 1interferon (IFN) and increased exposure to virus; physical factors; involving small body size, limited energy reserves and small airways. The interplay of these factors on the immune and anatomical structure of the respiratory system affects the physiology of the respiratory system leading to reduction in gaseous exchange thereby compromising respiration and eventually the disease [8].

This is particularly important in our consideration, noting the antigenic and phenotypic characteristics of viral agents on immune system of human body, in which acute respiratory infections may not be an exception and involving infants whose immune system are immature (still developing). Therefore, we may adduce the high frequency (pattern) and risk of contracting ARI among infants through exposure to pre-existing maternal/caregiver ARI as revealed by this study to principally, ignorance influenced increased exposure potential to the source of infection which is mainly viral in nature and discovered to be higher in the rural communities than their urban counterpart.

Our finding will therefore widen the horizon as an innovation in the etiological consideration regarding acute respiratory infection among infants vis-à-vis exposure potential to pre-existing maternal/caregiver acute respiratory infection occasioned by nursing care that will guide specific intervention strategies up to household level in resolution of the problem.

5. Conclusion

The existence of relationships between such predisposing or host factor in the patterns and risk of acute respiratory infection among infants is quite auspicious in the principles of nursing care and disease prevention and control of ARI. This calls for innovative prevention plan of action for effective management of infants' conditions to promote effective growth, development and health.

Recommendation

1) Community based sensitization programme on barrier nursing care techniques and personal hygiene practices for mothers/caregivers concerning acute respiratory infection should be given priority attention to reduce influence of exposure to pre-existing maternal/caregiver acute respiratory infection on infants' ARI burden.

2) Further studies should be carried out on this host factor in the patterns and risk of ARI among infants in a similar research design and setting for consisten-

cy and or complementarities.

3) Variability in exposure potential to maternal and caregiver pre-existing or concurrent ARI in terms of duration and differences in barrier nursing care should be looked into in the patterns and risk of ARI among infants in further studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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