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CONTACTS

For general inquiries about the journal
y.liu@jctres.com (Dr. Yao Liu)

For ethical/legal inquiries
y.liu@jctres.com (Dr. Yao Liu)

Assistant editor
d.deklerk@jctres.com (Mr. Daniel de Klerk)

For translation and proofreading services (English)
y.liu@jctres.com (Dr. Yao Liu)

For professional illustration services
megan.reiniers@gmail.com (Ms. Megan Reiniers)
markvart@planet.nl (Ms. LibaMarkvart)

For manuscript production inquiries
production@jctres.com

For advertisement inquiries
y.liu@jctres.com (Dr. Yao Liu)

Journal development editors
felicia@accscience.com (Ms. Felicia Wang)

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REVIEW ARTICLE

Association of appendectomy with colorectal cancer: a systematic review and meta-analysis

Busara Songtanin[1]*, Narisara Tribuddharat[2], Chanaka Kahathuduwa[1], Kenneth Nugent[1]

[1]Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA, [2]Department of Medicine, School of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

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**Corresponding author:*
Busara Songtanin
Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA.
Email: busara.songtanin@ttuhsc.edu

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ABSTRACT

Background: Appendectomy is a common surgical procedure done worldwide. The appendix is known as a sanctuary for commensal organisms in the gut, and an inflamed appendix may alter the gut microbiome, leading to inflammation and oncogenesis. An association between appendectomy and subsequent colorectal cancer development has been postulated; however, previous studies have differed in study design and results.
Method: We performed a systematic review and meta-analysis of studies evaluating the association between appendectomy and colorectal cancer in adults. A literature search of MEDLINE and EMBASE was conducted through September 2022. Search terms included "appendectomy" and "colon cancer" or "rectal cancer" or "colorectal cancer." Odds ratios and sensitivity analyses were calculated.
Result: Of the 541 studies identified in our search, 10 studies met our inclusion criteria. The eight papers that studied the association between appendectomy and colorectal cancer reported no association with the odds ratio (OR) of 1.30 (0.92, 1.83). However, studies on the association of appendectomy and proximal versus distal colon cancer reported a statistically significant increase in proximal colon cancer compared to distal colon cancer OR of 1.48 (1.29, 1.69).
Conclusion: Our study demonstrates that appendectomy is associated with the development of proximal colon cancer but not distal colon cancer.
Relevance for patients: Patients who have had an appendectomy should be aware of the potentially increased risk for colon cancer. Consequently, they should provide this information during routine clinic visits, especially if they are having gastrointestinal symptoms.

1. Introduction

According to the World Health Organization, colorectal cancer was the third most common cancer worldwide with approximately 1.93 million cases reported in 2020. Despite increasing screening measures, colorectal cancer remained the second most common cause of cancer death (916,000 deaths in 2020) [1]. Identifying possible risks for colorectal cancer is important because colorectal cancer screening can result in early detection. Common risk factors include age over 50 years, a family history of colorectal cancer, certain predisposing genes, and long-standing inflammatory bowel disease. Potentially modifiable factors include obesity, smoking, and heavy alcohol consumption [2]. Surprisingly, several studies have suggested that an appendectomy is a risk factor for developing colorectal cancer; however, this association has not been established [3-5].

Appendectomy is a common surgical procedure done worldwide. The previous studies have shown appendectomy can alter the gut microbiome, depriving the colon of a backup reserve of diverse commensal bacteria in case of diseases, such as diarrhea [6]. It may also

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alter the balance that controls immune tolerance from gut antigens and gut inflammation, a process considered to be a mechanism for the development of colorectal cancer [7]. Appendectomy may be a potential risk factor in developing colorectal cancer; however, differences in study design, such as the definition of the interval between appendectomy and the initial diagnosis of colorectal cancer, follow-up period, and location of colorectal cancer, need consideration. Therefore, we performed a systematic review and meta-analysis to evaluate the association between appendectomy and the development of colorectal cancer.

2. Methods

We conducted this meta-analysis according to Cochrane's manual of diagnostic test accuracy, and the manuscript was prepared according to the preferred reporting items for systematic reviews and meta-analysis of diagnostic test accuracy (PRISMA-DTA) guidelines [8,9].

A literature search of MEDLINE and EMBASE databases was conducted from their inception through September 2022. Search terms included (a) appendectomy, (b) colorectal cancer, colon cancer, and rectal cancer. Only studies evaluating adult population were included in the study. Case series, case reports, and non-English publications, and studies with appendiceal carcinoma and mucinous appendiceal neoplasm were excluded from the study. The titles and abstracts were reviewed by two independent authors (B.S. and N.T.). Discrepancies were resolved through discussion between the two independent authors and the senior author (K.N). Two independent authors compiled data from each study, including study characteristics, study population characteristics, and study results (B.S. and N.T.). Study characteristics included author, year of publication, start and end dates for data collection, country, and type of study design. Study population characteristics included number of patients, age, gender, number of patients who underwent appendectomy, number of control patients (those without appendectomy), number of colorectal cancers, location of colon cancers (classified as proximal colon which includes cecum, ascending colon, hepatic flexure, and transverse colon and distal colon which includes splenic flexure, descending colon, and sigmoid colon) and rectal cancer if data were available), and number of patients without colorectal cancers. The quality of each study was independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale [10]. Any discrepancies were resolved through discussion between the two independent authors with the senior author (K.N.).

2.1. Statistical analysis

A DerSimonian-Liard random-effects meta-analysis was performed using the "meta" package (version 5.0-1) in R statistical software (version 4.2.2) to examine the pooled odds ratio representing the associations between colorectal cancer and the history of appendectomy. Additional random-effects meta-analyses were performed to pool the odds ratios of studies examining the associations between appendectomy based on the anatomical site of colorectal cancer (i.e., proximal vs. distal colon cancer vs. rectal cancer). The proximal colon consists of cecum, ascending colon, hepatic flexure, and transverse colon whereas the distal colon consists of splenic flexure, descending colon, and sigmoid colon.

The consistency of the findings of all meta-analyses was further examined using leave-one-out sensitivity analyses. The likelihood of publication bias was explored using funnel plots, and the effect sizes of missing (i.e., unpublished/unreported) studies were imputed through the trim-and-fill method [11,12]. Funnel plot asymmetry was confirmed using Egger's tests [13]. Heterogeneity of effect sizes was quantified by calculating the Higgins' I^2 statistic [14,15]. Meta-regression analyses were not attempted due to the small number of studies included in each meta-analysis [15,16].

3. Results

Figure 1 provides a graphical representation of the study screening and selection process. A total of 919 articles were found using the above search criteria. After removal of duplicates, 541 articles were evaluated. Of these, 23 articles were potentially relevant to the study goals. Thirteen studies were removed because the study was a non-English publication (n = 3), used the same study cohort (n = 1), was a review article (n = 1) or a letter to the editor (n = 1), or had missing data (n = 7). Therefore, 10 studies were included in this meta-analysis [4,5,17-24]. Table 1 reports the characteristics of each study. Of these studies, one was abstract, and nine were full articles. A total of 39,711 colorectal cancers and a total of appendectomies 384,278 were analyzed. Two studies did not classify patients based on the specific location but reported results just as colorectal cancer [5,22]; eight studies classified patients based on a specific location of colorectal cancer [4,17-21,23,24]. Table S1 demonstrates an association

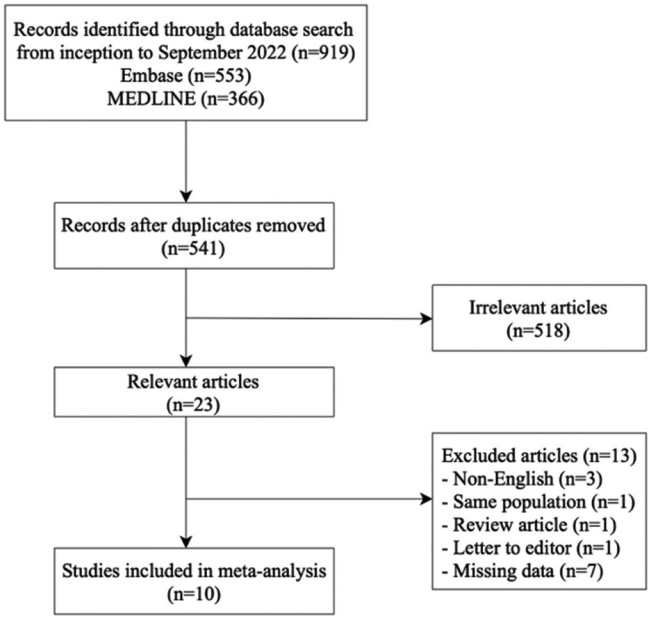

Figure 1. A visual representation of the search strategy.

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Table 1. Characteristics of studies evaluating the association between appendectomy and colorectal cancer

Author	Year	Country	Publication type	Study type	Number of patients (n)	Start date	End date	Mean age (year)	Male (n)	Number of appendectomy (n)	Number of CRC (n)	Duration between appendectomy and time of diagnosis of CRC
Abraham	2020	Hungary	Full paper	Retrospective	604	2015	2017	66.5±11.5	350	100	604	NR
Ergul	2009	Turkey	Full paper	Retrospective	621	NR	NR	NR	410	205	455	3 years
Friedman	1990	USA	Full paper	Retrospective	7625	1964	1972	40.2	3256	1590	7625	9.8 years
Lee	2018	Korea	Full paper	Retrospective	707633	2002	2015	41.7±14.7	347411	16094	4324	No lag period
Lee	2021	Korea	Full paper	Retrospective	486844	Jan 2005	Dec 2013	32.4±17.0	284546	243422	2804	1 year
Mandi	2021	Hungary	Full paper	Retrospective	901	Jan 2018	Feb 2021	70.2	515	133	457	40.9 years
Qu	2021	China	Full paper	Retrospective	20739	Jan 2014	Dec 2018	61.5	12360	794	20739	NR
Shi (Cohort 1)	2021	Hongkong	Abstract	Retrospective	136953	Jan 2000	April 2020	NR	NR	44587	748	1 year
van den Boom	2021	Netherlands	Full paper	Prospective	7136	1989	1993	69.8±9.3	2836	1374	277	NR
Wu	2015	Taiwan	Full paper	Retrospective	379619	1997	1999	31.8	196317	75979	1678	30 months

CRC: Colorectal cancer; NR: Not reported

between appendectomy and colorectal cancer in each study group. These studies did not report the indication for appendectomy or the histology of the resected appendices.

3.1. Association between colorectal cancer and history of appendectomy

Eight studies reported a comparison of the history of appendectomy and development of colorectal cancer compared with control patients who underwent appendectomy but did not develop colorectal cancer. The number of patients with colorectal cancer was 11,897, and the number of control patients (i.e., those without colorectal cancer) was 1,873,936.

Our result demonstrated that the association between colorectal cancer and a history of appendectomy was not significant (OR = 1.30 [95% CI: 0.92, 1.83], $P = 0.132$; Figure 2). The observed result remained consistent in all leave-one-out sensitivity analyses except with the omission of Lee *et al.* (2018) which resulted in a significant association (OR = 1.42 [95% CI: 1.01, 1.99], $P = 0.041$). The funnel plot was asymmetric indicating possible publication bias (Figure S1). Three effect sizes were imputed using trim-and-fill method to restore funnel plot symmetry, and reanalysis of the data including these three effect sizes revealed a significant association between colorectal cancer and a history of appendectomy (OR = 1.79 [95% CI: 1.19, 2.71], $P = 0.005$). Between-study heterogeneity was high ($I^2 = 97.8\%$; $\tau^2 = 0.226$; $P < 0.001$). Meta-regression analyses were not attempted due to the small number of studies included in the study.

3.2. Association between proximal versus distal colon and rectal cancer and history of appendectomy

Four studies were analyzed to compare the history of appendectomy and the development of proximal colon cancer with the history of appendectomy and development of distal colon cancer and rectal cancer. In this subgroup analysis, the number of proximal colon cancers was 4,647, and the number of distal colon cancers and rectal cancers was 17,608. Our result demonstrated that the association between proximal or right-sided colon cancer and a history of appendectomy was significant (OR = 1.48 [95% CI: 1.29, 1.69], $P < 0.0001$; Figure 3). The funnel was symmetrical, indicating no publication bias (Figure S2), and study heterogeneity was low ($I^2 = 10.80\%$; $\tau^2 = 0$; $P < 0.0001$). Meta-regression analyses were not attempted due to the small number of studies included in the study.

3.3. Association between colon versus rectal cancer and history of appendectomy

Six studies were analyzed to compare a history of appendectomy and development of colon cancer with rectal cancer. The number of colon cancer was 4676; the number of rectal cancers was 3078. Our result demonstrated that the association between colon cancer and a history of appendectomy was not significant (OR = 0.96 [95% CI: 0.67, 1.37], p = 0.01; Figure 4). The funnel was symmetric indicating no publication bias (Figure S3) and heterogeneity was moderate ($I^2 = 64.70\%$; $\tau^2 = 0.13$; $P = 0.01$).

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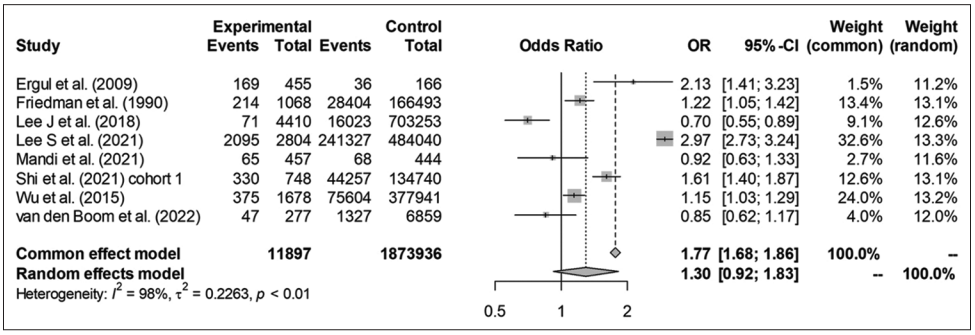

Figure 2. Forest plot of appendectomy in patients with colon cancer in comparison to control patients.

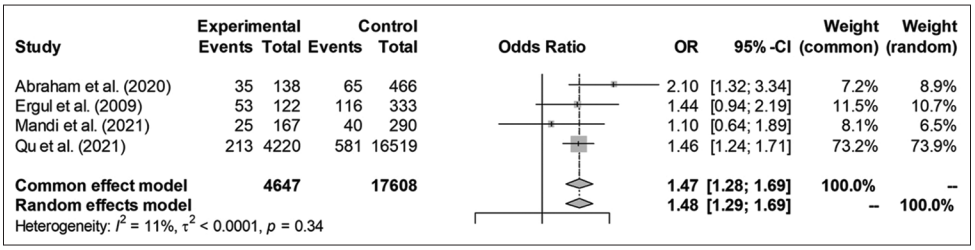

Figure 3. Forest plot of appendectomy in proximal colon cancer in comparison to distal colon cancer.

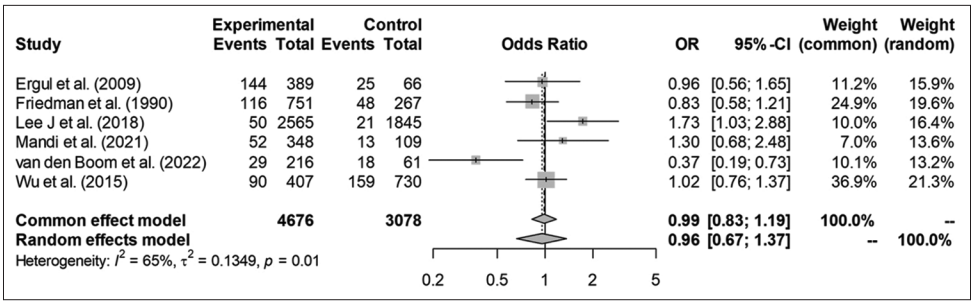

Figure 4. Forest plot of appendectomy in patients with colon cancer in comparison to patients with rectal cancer.

3.4. Quality assessment

During the article screening, there was good agreement between the two authors as demonstrated by a Newcastle-Ottawa score, shown in Tables S2 and S3. Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures.

4. Discussion

In this study, patients with distal colon and rectal cancer were compared to patients with proximal colon cancer because the cancers in these two locations have different clinical and genetic/molecular features. The prevalence of proximal colon cancer (40.4%) is higher than distal colon cancer (28.9%) and rectal cancer (30.7%) [25]. A study based on the SEER database reported that proximal colon has a worse prognosis compared than distal colon cancers, but the reason remains unclear [26]. Shi *et al.* reported a longitudinal study of 43,976 appendectomy cases and 85,179 age- and gender-matched non-appendectomy controls and the development of colon cancer [27]. During the 20-year follow-up period, the incidence of colorectal cancer was 73.1/100,000 person-years in the appendectomy group and 39.7/100,000 person-years in the control group. The overall risk of the development of colorectal cancer was increased by 73% in appendectomy cases, and these cases had significantly higher risk for the development of cancer in the proximal colon than in the distal colon and rectum.

This meta-analysis included 384,297 appendectomies and 39,711 colon cancer cases and demonstrated that appendectomy has a significant association with proximal colon cancer (OR = 1.48 [95% CI: 1.29, 1.69], P < 0.0001) with low heterogeneity between studies. In the analysis which compared the frequency of appendectomy in all patients with colon cancer with the frequency of appendectomy in healthy controls, the association was not significant but did become significant when the Lee J study was excluded [19]. This might be explained by the effect of a lag period from appendectomy to the diagnosis of colorectal cancer. Lee J reported a positive association with no lag period (HR = 1.44 [95% CI: 1.14, 1.83]) but no association with a 3-year lag period (HR = 0.75 [95% CI: 0.50, 1.13]). Lai

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et al. reported that 16 patients out of 1873 patients with acute appendicitis were found to have colon cancer [28]. The median time interval before diagnosis was 5.8 months. The odds ratios of having an increase in cancer incidence were 38.5-fold in patients older than 40 with acute appendicitis. Consequently, older patients with acute appendicitis should be evaluated for colon cancer.

Since the proximal colon and distal colon have different embryological origins, this could contribute to differences in the prevalence and prognosis in colon cancers in these two regions. Furthermore, there are differences in the carcinogenic pathway and gene expression in proximal and distal colon cancers; proximal tumors more often have a microsatellite instable pathway and hypermutated DNA, whereas distal colon tumors often have large chromosomal alterations [29,30]. Proximal colon tumors have low chromosomal instability, whereas distal colon tumors have high chromosomal instability. These proximal cancers are associated with older age, higher tumor grade, mucinous differentiation, and dense infiltration of lymphocytes [29]. The genes that are overexpressed in these tumors include genes associated with inflammatory reactions and drug metabolism. Genetic alterations include microsatellite instability, hypermethylation, mutations in key tumor genic pathways, and BRAF mutants. These pathways may be stimulated by bacterial toxins and mutagenic metabolites and lead to tumor development.

The association of appendectomy with the development of proximal colon cancer requires consideration of the function of the appendix and the potential changes in colonic health associated with appendectomy. The mucosa in the appendix contains plasma cells which secrete IgA and IgG; it is the primary site for IgA production. The submucosa contains aggregates of lymphocytes, and the morphology is similar to the concentrated lymphoid tissue in Peyer's patch in the ileum. The appendix is a repository for commensal gut bacteria, such as *Firmicutes, Proteobacteria, Bacteroidetes, Fusobacteria,* and *Actinobacteria* [31,32]. Its immune function probably depends in part on these commensal organisms [6]. The existence of biofilm in the appendix has beneficial effects on the entire digestive system [6] and is thought to act as a sanctuary for commensal bacteria and to facilitate their reinoculation of the gut after a gastrointestinal infections and possibly episodes of antibiotic treatment. The changes in commensal bacteria and the development of "abnormal" biofilms could lead to alterations in colonic health and function [33].

The development of colorectal cancer is explained in part by alterations in genetic factors. However, environmental factors, such as local inflammation and microbiota, may also have an important role [24]. A study of the appendiceal tissue revealed increased numbers of natural killer (NK) T cells that can produce cytokines following activation [6]. The evidence of immune cells in appendiceal tissue is also supported by another study by Yaun-Kun which demonstrated that patients with appendiceal inflammation have lower NK cells; patients with colorectal cancer and a normal appendix have low NK cells [34]. The cells have a suppressor function and could limit the development and proliferation of malignant cells.

With the novel concept of gut biofilm and dysbiosis in association with both benign and colorectal cancer due to ongoing colonic inflammation, alteration of intestinal biofilms after appendectomy has been proposed as a possible pathophysiology underlying colorectal cancer [33]. Dejea identified polymicrobial bacterial biofilms in 89% of proximal tumors but in only 12% of the distal tumors [35]. Bacterial biofilms were associated with increased epithelial permeability and activation of IL-6 and Stat3 [35]. In the normal colon mucosa, biofilms were associated with increased crypt epithelial cell proliferation and possibly initiate pro-carcinogenic tissue inflammation. In addition, IL-6 and Stat3 have been associated with increased epithelial proliferation, apoptosis, and/or angiogenesis. These authors suggest that the presence and organization of biofilm are important factors in the pathogenesis of colorectal cancer pathogenesis and this process may not depend on the types of bacteria in biofilm. Dejea reported that biofilms found in colorectal cancer patients had bacterial invasion into the tumor mass and this possibly changes tissue biology by enhancing cellular proliferation and oncogenic transformation. This feature was not detected in biofilm-negative tumors [35]. Shi and coinvestigators also analyzed the gut microbiome in 157 appendectomy cases and 157 normal controls using metagenomic sequencing [27]. The patients with appendectomy had a significant increase in the *Fusobacterium* phylum. Patients with appendectomy had lower microbiota diversity, and these changes persisted over a 2-year follow-up period. These changes were more pronounced in older patients (>50 years). Patients with appendectomy had an enrichment of colorectal cancer-associated species in the gut. There were 11 enriched species, and seven of them have been associated with colorectal cancer. Five possibly protective bacteria were depleted in these samples. Microbial genes were analyzed to determine the metabolic pathways in these microbiomes. In appendectomy cases, the pathways for the biosynthesis of deoxyribonucleotides, peptidoglycan, L-glutamine, L glutamate, and pyrimidine deoxyribonucleotides were increased; these pathways have been reported as cancer promoting. The biosynthesis L-proline was decreased, and this compound is thought to be protective. Overall, this study demonstrates that appendectomy causes microbial dysbiosis with increases in colorectal cancer-promoting bacteria and depletion of possibly beneficial microbes [27].

In summary, the association between appendectomy and the proximal colon cancer has several possible explanations. First, the proximal colon has higher levels of microbial biofilms (89%) than the distal colon (18%). The appendix is located on the cecum and the appendectomy can alter the microbiome and result in dysbiosis and bacterial invasion which stimulates tumor formation. Second, the loss of immune function after appendectomy leads to changes in the interaction between microbiota and colonic mucosa. Clinical investigations need to determine if there is a consistent alteration in colonic flora associated with pathogenic biofilms. This might lead to prospective studies on the development of colon cancer in patients with these changes in flora and eventually to determine whether or not strategies to replace pathogenic flora with normal flora have potential benefit [36].

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This meta-analysis has several limitations. First, the total number of studies in this meta-analysis is relatively small. Second, there are differences in the time interval between appendectomy and the diagnosis of colorectal cancer, and there are differences in study design. The lag time might have a role in tumor development [17]. Third, the age of patients when they were diagnosed with colorectal cancer was not available; therefore, it is unclear if patients who undergo appendectomy should have colorectal cancer screening earlier than general populations. There were no studies on the association of mucinous neoplasm of appendix and colon cancer or on the type of appendicitis, that is, acute on chronic appendicitis, and colon cancer.

5. Conclusions

This meta-analysis demonstrates an association of appendectomy the development of proximal colon cancer but not distal colon cancer. This study suggests that clinicians should consider the possibility of colorectal cancer in patients with prior appendectomy who develop new and persistent constitutional or gastrointestinal symptoms regardless of age.

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Conflicts of Interest

The authors declare they have no competing interests.

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REVIEW ARTICLE

Association of appendectomy with colorectal cancer: a systematic review and meta-analysis

Supplementary File

Table S1. Association between appendectomy and colorectal cancer

Association between appendectomy compared with CRC	Number of studies included	Odds ratio (95% CI)
Appendectomy versus CRC and non-CRC	8	1.30 (0.92, 1.83)
Appendectomy versus proximal and distal colon cancer	4	1.48 (1.29, 1.69)
Appendectomy versus colon and rectal cancer	6	0.96 (0.67, 1.37)

CRC: Colorectal cancer

Table S2. The Newcastle-Ottawa quality assessment scale of the included cohort studies

Author (year)	Selection				Comparability	Outcome			Total score
	Representativeness	Selection of the non-exposed cohort	Ascertainment	Endpoint not presented at start	Comparability (confounding)	Assessment of outcome	Follow-up duration	Adequacy of follow-up	
Abraham (2020)	★	★	★	★	0	★		★	7
Friedman (1990)	★	★	★	★	★	★		★	8
Lee (2018)	★	★	★	★	★	★		★	8
Lee (2021)	★	★	★	★	★	★	0	★	7
Mandi (2021)	★	★	★	0	★	★	★	★	7
Shi (2021)	★	★	★	★	★	0	★	★	7
van den Boom (2021)	★	★	★	★	★	★	★	★	8
Wu (2015)	★	0	★	★	★	★	★	★	7

Table S3. The Newcastle-Ottawa quality assessment scale of the included case–control studies

Author (year)	Selection				Comparability	Outcome			Total score
	Representativeness	Adequate definition	Selection of controls	Definition of controls	Comparability	Assessment of exposure	Method of assessment	Non-response rate	
Ergul (2009)	★	★	★	★	0	★	★	★	6

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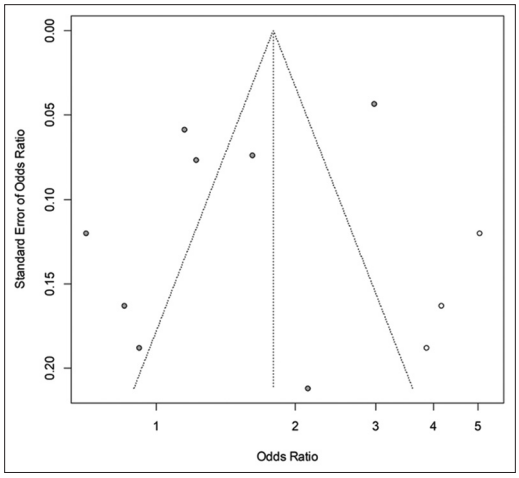

Figure S1. Funnel plot of the association between appendectomy and colorectal cancer versus non-colorectal cancer group.

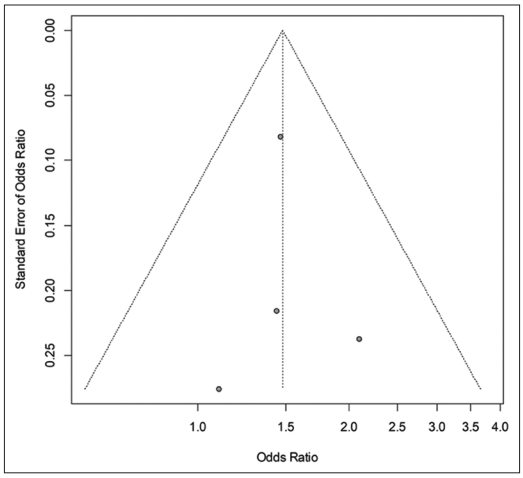

Figure S2. Funnel plot of the association between appendectomy and proximal colon cancer versus distal colon cancer.

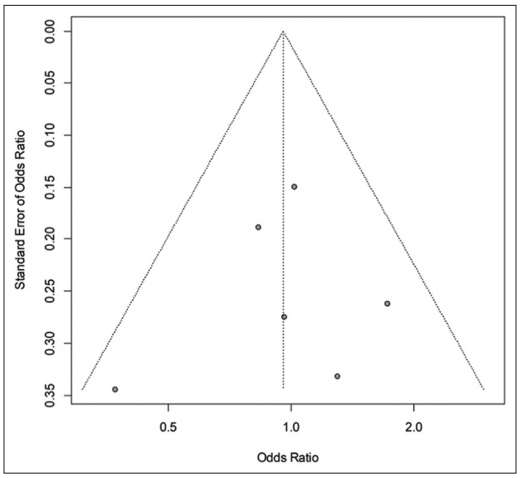

Figure S3. Funnel plot of the association between appendectomy and colon cancer versus rectal cancer.

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ORIGINAL ARTICLE

Comparison of bronchodilator response between Dosivent® and Aerochamber Plus® Flow-Vu® chambers in patients with bronchial hyperreactivity

Zichen Ji[1,2], Ángela Gómez-Sacristán[1,2], Walther Iván Girón-Matute[1,2]*, Raquel Terán-Marcos[1,2], Luis Puente-Maestu[1,2,3]

[1]Department of Respiratory, Gregorio Marañón General University Hospital, 28007 Madrid, Spain, [2]Gregorio Marañón Hospital Biomedical Investigation Institute, 28007 Madrid, Spain, [3]Department of Medicine, Faculty of Medicine, Complutense University of Madrid, 28040 Madrid, Spain.

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**Corresponding authors*
Walther Iván Girón-Matute
Department of Respiratory, Gregorio Marañón General University Hospital,
28007 Madrid, Spain.
Tel.: +34 91 586 83 36
E-mail: walter_giron2@hotmail.com

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ABSTRACT

Background: Aerochambers are used for the administration of inhaled drugs. Dosivent® is a previously unstudied chamber. This study aimed to validate the Dosivent® chamber against the widely used Aerochamber Plus® Flow-Vu®.

Methods: We conducted a non-randomized, open-label, cross-over-controlled, and clinical trial (NCT05821868) in 50 patients with a known positive bronchodilator test. Bronchodilator washout was performed according to standard recommendations. Fifteen minutes after the administration of 400 µg of salbutamol with either chamber, the changes in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were measured. The agreement was measured by the intraclass correlation coefficient and Bland–Altman graphical analysis. Participants' satisfaction with the chamber was assessed with the FSI-10 questionnaire.

Results: The mean participant age was 58.0 (SD = 18.5) years, half were women, and only 31 (62%) participants had an FEV1/FVC of <0.7. The median increases in FEV1 obtained with the Aerochamber Plus® Flow-Vu® and Dosivent® were 0.28 L (interquartile range [IQR]: 0.21 – 0.38) and 0.29 L (IQR: 0.20 – 0.43), respectively, and the median increases in FVC were 0.29 L (IQR: 0.19 – 0.37) and 0.28 L (IQR: 0.19 – 0.45). The intraclass correlation coefficient for increases in FEV1 was 0.865, and it was 0.820 for increases in FVC. The median FSI-10 questionnaire score was 42 (IQR: 37 – 47) with Aerochamber Plus® Flow-Vu® and 44 (39 – 48) with Dosivent® ($P < 0.001$).

Conclusions: Our study revealed a strong agreement between salbutamol responses when utilizing both the Dosivent® and Aerochamber Plus® Flow-Vu® chambers. This suggests that these devices are interchangeable and can be effectively employed in routine clinical practice.

Relevance for Patients: For patients using inhaled medications, this study provides reassurance regarding the equivalence of the Dosivent® chamber with the widely used Aerochamber Plus® Flow-Vu®. This provides patients with more options for device selection, potentially improving convenience and satisfaction with their inhalation therapy. Patients and healthcare providers can consider the Dosivent® chamber as a viable alternative, which may positively impact treatment adherence and overall respiratory health management.

1. Introduction

Inhaled therapy is an airway administration route for bronchodilator and anti-inflammatory drugs that are widely used in patients with obstructive respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD) [1,2]. It is also often used in pulmonary function laboratories for bronchodilator tests [3,4]. This method of administration allows a

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direct deposit of drugs into the airway and, therefore, reduces the amount of medication needed, minimizing the systemic effect of the drugs [5].

Metered dose inhalers (MDIs) present some advantages compared with other devices: They require no threshold inspiratory flow to trigger the release of the active compound, and they are cheap [6-8]. However, their use requires dexterity to complete the required sequential steps to achieve a correct inhalation of the medication; in particular, they require coordination between the pulsation of the cartridge and the inhalation. Incorrect completion of one or more steps in using an MDI can substantially reduce the administrated medication delivery and consequently its effectiveness and safety. Numerous studies have demonstrated that 50 – 100% of patients do not use their inhaler devices correctly [9]. To overcome this limitation, MDIs are frequently used with add-on devices referred to as inhalation chambers ("chambers," in the context of inhalation devices) [10]. Chambers act as reservoirs and reduce the speed at which the aerosol enters the mouth. This makes using the inhaler easier and helps ensure that more of the medication reaches the lungs [11].

Performing spirometry before and after the inhalation of bronchodilators (bronchodilator response [BDR] testing) is in diagnosing asthma and COPD [12,13]. In most laboratories, the bronchodilator drug (usually salbutamol/albuterol) is administered through a chamber. The Dosivent® inhalation chamber is designed to optimize the delivery of inhaled bronchodilators and corticosteroids in the treatment of respiratory diseases.

This study was conducted to compare the efficacy, as measured by changes in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC), of salbutamol inhaled with the Dosivent® chamber versus the widely used Aerochamber Plus® Flow-Vu® in patients with a positive BDR, as Dosivent® is a previously unstudied chamber.

2. Materials and Methods

2.1. Design

We conducted a non-randomized, open-label, crossover-controlled, and clinical trial in 50 patients with a previous positive BDR. The protocol was approved by the Drug Research Ethics Committee of the Gregorio Marañon General University Hospital (code 03/2022) and registered with registration number NCT05821868. All participants provided written informed consent before any study procedure. During the study, the principles of the Declaration of Helsinki and the current standards of Good Clinical Practice were followed.

2.2. Study population

Patients over 18 years of age were included who attended our center for a bronchodilator test, gave a positive result in this test, and provided written informed consent for participation in this study. Patients were excluded if Grade A quality spirometry was not obtained according to the classification in current guidelines [13] and, in the opinion of the investigator, performing a bronchodilator test could pose a risk to the patient or interrupting the usual bronchodilator treatment could worsen the underlying respiratory pathology.

2.3. Sample size calculation

To achieve a statistical power of 80% and a significance level of a two-tailed $P < 0.05$, 45 patients were necessary for the study to detect a 5% of difference. A loss of 10% was anticipated, rendering a sample of 50 participants.

2.4. Study interventions

Before the BDR test, participants were asked to interrupt their usual bronchodilator medication according to standard washout recommendations [13]. On the first visit, after checking that the patient had followed the washout instructions, baseline spirometry was performed [13]. This was followed by the inhalation of 400 μg of salbutamol MDI through the Aerochamber Plus® Flow-Vu® chamber. A postbronchodilator spirometry was performed 15 min later. Patients then completed the Feeling of Satisfaction with Inhaler (FSI-10) questionnaire, and washing-out instructions were given for the next visit. Two days later, a similar BDR test was performed, this time using the Dosivent® chamber.

The main outcomes were changed in FEV1 and FVC, measured as absolute value and percentage (i.e., [postbronchodilator FEV1 or FVC – prebronchodilator FEV1 or FVC]/prebronchodilator FEV1 or FVC).

The secondary outcome was the difference in FSI-10 score between the two chambers.

Other variables such as demographic data, underlying lung disease, and adverse effects were collected from medical records and the anamnesis on the day of the bronchodilator tests.

2.5. Statistical analysis

Quantitative variables are described as mean and standard deviation (SD) or should the normality assumption not hold, median, and interquartile range (IQR). The Friedman test was used for two-tailed statistical comparisons of between-groups changes in FEV1, FVC, and FSI-10 questionnaire score. To evaluate the agreement between BDR with both chambers, the intraclass correlation coefficient and Bland–Altman graphic analysis were performed. For the latter, the ordinates were the difference between the Dosivent® and Aerochamber Plus® Flow-Vu®. Statistical significance was established at $P < 0.05$ for all comparisons. Stata version 15 was used to generate the Bland–Altman plots. All other analyses were performed with SPSS version 26.

3. Results

Fifty-six patients were invited to participate in the study. Of these, 50 provided written informed consent and were included in the study. No participant dropped out of the study (Figure 1).

Twenty-five (50%) of the participants were men. The mean age was 58 (SD 18) years, the mean height was 1.64 m (0.1), the mean weight was 75.1 kg (17.5), and the mean body mass index

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was 27.9 kg/m^2 (6.0). The mean prebronchodilator FEV1 and FVC were 2.11 L (0.83) and 3.15 L (0.97), respectively. Thirty-one participants (62%) had a prebronchodilator FEV1/FVC < 0.70. Regarding pulmonary disease, 14 participants (28%) had COPD, and 22 (44%) had bronchial asthma (Table 1).

The median increases in FEV1 obtained with the Aerochamber Plus® Flow-Vu® and Dosivent® were 0.28 L (IQR: 0.21 – 0.38) and 0.29 L (0.20 – 0.43), respectively; these differences were non-significant (Table 2). The median increases in FVC were 0.29 L (0.19 – 0.37) and 0.28 L (188 – 453), also non-significant (Table 3).

The agreement in BDR between the chambers was excellent, with intraclass correlation coefficients of 0.865 and 0.820, respectively, for FEV1 and FVC. Figures 2 and 3 show the Bland–Altman graph for the increases in FEV1 and FVC with both chambers. Regarding FEV1, 3 participants (6%) were outside the lower limit of agreement. For FVC, 3 participants (6%) were outside the limits of agreement: Two below the lower limit and one above the upper limit.

Participants' satisfaction favored the Dosivent®, with a median FSI-10 score of 44 (IQR: 39 – 48) compared to 42 (IQR: 37 – 47) with the Aerochamber Plus® Flow-Vu®; this difference was statistically significant (P < 0.001). No adverse events were observed during the study.

Table 1. Subjects' demographic and clinical characteristics

Characteristic	N or mean	% or SD
Male	25	50
Age	58.0 years	18.5
Height	164.0 cm	10.0
Weight	75.1 kg	17.5
BMI	27.9 kg/m^2	6.0
FEV1 prebronchodilator	2.11	0.83
FVC prebronchodilator	3.15	0.97
Obstruction prebronchodilator	31	62
COPD	14	28
Asthma	22	44

BMI: Body mass index; FEV1: Forced expiratory volume in the first second; FVC: Forced vital capacity; COPD: Chronic obstructive pulmonary disease

4. Discussion

In our study, we observed a high level of concordance [14,15] in the BDR after the inhalation of 400 µg of salbutamol through both the Dosivent® and Aerochamber Plus® Flow-Vu® chambers.

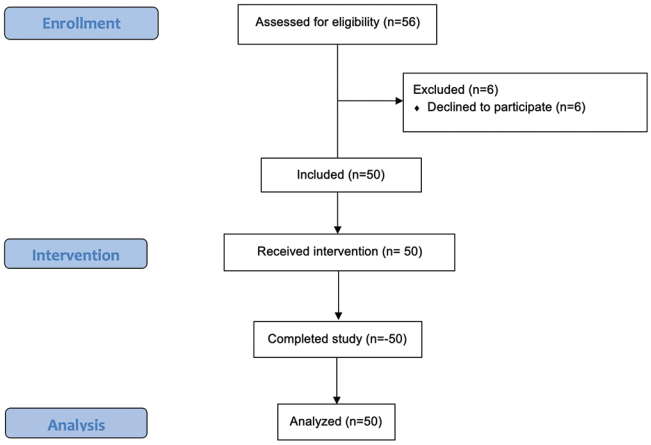

Figure 1. CONSORT diagram.

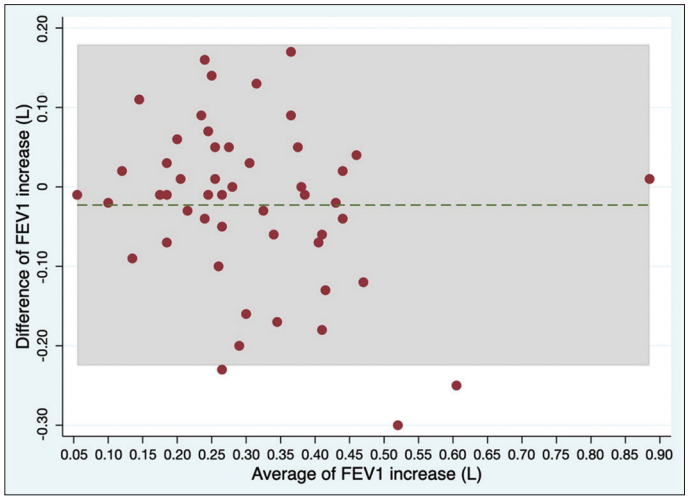

Figure 2. Bland-Altman plot representing concordance between forced respiratory volume during first second increase with Aerochamber Plus® Flow Vu® and Dosivent®.

Table 2. FEV1 and FEV1 increase comparison according to aerochamber

Median (IQR)	FEV1 pre-BD L	FEV1 post-BD L	FEV1 increase L	FEV1 increase %
Aerochamber®	1.97 (1.51 – 2.66)	2.27 (1.72 – 3.04)	0.28 (0.21 – 0.38)	13.4 (11.6 – 17.2)
Dosivent®	1.96 (1.51 – 2.66)	2.30 (1.75 – 3.02)	0.29 (0.20 – 0.43)	13.8 (12.1 – 17.3)
P-value	0.668	0.258	0.248	0.777

IQR: Interquartile range; FEV1: Forced respiratory volume during first second; BD: Bronchodilator.

Table 3. FVC and FVC increase comparison according to aerochamber

Median (IQR)	FVC pre-BD L	FVC post-BD L	FVC increase L	FVC increase %
Aerochamber®	3.10 (2.34 – 3.81)	3.43 (2.57 – 4.01)	0.29 (0.19 – 0.37)	10.6 (5.3 – 12.5)
Dosivent®	3.05 (2.35 – 3.83)	3.44 (2.56 – 4.07)	0.28 (0.19 – 0.45)	11.6 (5.9 – 14.1)
P-value	0.662	0.090	0.886	0.777

IQR: Interquartile range; FVC: Forced vital capacity; BD: Bronchodilator.

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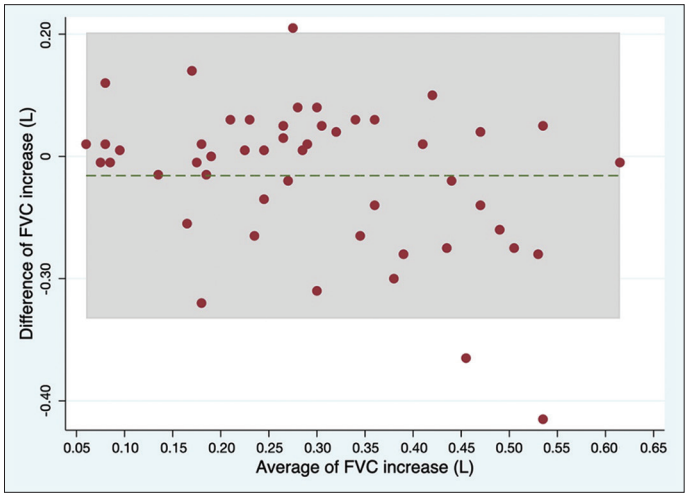

Figure 3. Bland-Altman plot representing concordance between forced vital capacity increase with Aerochamber Plus® Flow Vu® and Dosivent®.

In addition, we observed that the bronchial response to salbutamol was reproducible over a 2-day period.

In the literature, few comparative studies exist between different chambers, and no previous study has included Dosivent®. Most, like ours, have compared the increase in FEV1 after the administration of a bronchodilator through different devices [16-18]. Some have also compared the FEV1 change with different chambers and the direct administration of the MDI [16]. We used the Aerochamber Plus® Flow-Vu® for comparison because it is commonly used. It has also been widely studied in patients of different ages, with different respiratory diseases, and whose characteristics are well known both *in vitro* and *in vivo* with different inhalers [19-24]. We found excellent agreement according to the intraclass correlation coefficient. The Bland–Altman plot also showed good agreement, with only 6% of the point outside the 95% confidence interval.

We found no comparative study on the satisfaction of patients with different chambers. In our study, we found a slightly but significantly higher FSI-10 score with the Dosivent® relative to the Aerochamber Plus® Flow-Vu®. The FSI-10 questionnaire evaluates the subjective satisfaction of patients with inhalers and has been widely used for patients with different pulmonary pathologies [25-27]. It was not specifically designed to evaluate inhalation chambers, but its questions refer to the ease of use of the devices and chambers.

The main strength of our study is that we included patients with both known and newly diagnosed diseases, as well as patients of both sexes, with and without baseline airflow obstruction.

Our study also has limitations. First, since it was not randomized, it could have been influenced by the moment in which the tests were performed. However, only one patient had a negative BDR (different with each chamber), the washout procedure was similar for the two tests, and the sessions were separated only by 2 days. Second, the sample size did not allow sufficient statistical power to analyze the subgroups of participants. Third, we have only analyzed the change in FEV1 with the administration of salbutamol 400 µg. Other doses of salbutamol and other bronchodilators should be studied in future studies.

This study may impact clinical practice since the previously non-validated Dosivent® chamber showed similar performance to another commonly used inhalation chamber, and it seems more satisfactory for users.

5. Conclusions

The Dosivent® chamber demonstrated excellent agreement with the Aerochamber Plus® Flow-Vu® in terms of the increase in FEV1 and FVC during a bronchodilator test. Therefore, in routine clinical practice, it is viable to use both chambers interchangeably contingent on the preferences of the patient and professional.

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Conflicts of Interest

L.P.-M. has received funding from GSK, Chiesi, and Sanofi and has received consulting fees from MSK. All other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Appropriate patient selection and overall survival after transarterial radioembolization in colorectal adenocarcinoma liver metastases

Sharmeen Mahmood[1], Garo Hagopian[1], Ben Sadeghi[2], Jeffrey V. Kuo[3], David K. Imagawa[3], Dayantha Fernando[2], Nadine Abi-Jaoudeh[2†], Farshid Dayyani[1*†]

[1]Department of Medicine, Division of Hematology/Oncology, University of California Irvine, Orange, California, United States of America, [2]Department of Radiological Sciences, Division of Vascular and Interventional Radiology, University of California Irvine, Orange, California, United States of America, [3]Department of Radiation Oncology Orange, University of California Irvine, California, United States of America, [4]Department of Surgery, Division of Hepatobiliary Surgery, University of California Irvine, Orange, California, United States of America
[†]These authors contributed equally to this work.

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**Corresponding author:*
Farshid Dayyani
University of California Irvine, Department of Medicine/Division of Hematology/Oncology, 200 S Manchester Ave, Orange, California (CA) 92868, United States of America.
Tel: +1 714 456 8161
Fax: +1 714 456 2242
Email: fdayyani@hs.uci.edu

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ABSTRACT

Background and Aim: The objective of this study was to describe the overall survival (OS) with transarterial radioembolization (TARE) for patients with colorectal adenocarcinoma liver metastases (CRLM) treated at an academic center with a dedicated multidisciplinary liver tumor board (MTB).
Methods: Single institution retrospective study of consecutive patients with CRLM undergoing TARE with mainly Y90 resin spheres between 01/2016-07/2020.
Results: Fifty-five patients were included in the study. Median age was 60 years (range 36–84), 61.8% were female, Eastern Cooperative Oncology Group 0–1 = 90.9%. The median time from diagnosis to first TARE was 16.4 months (1.7–95.6) and 36.4% were treated within the first 12 months of diagnosis. With a median follow-up of at least 2 years, the median OS from the date of diagnosis and first TARE was 43.2 months (29.5–68.7) and 16.7 months (9.9–35.2), respectively.
Conclusions: The observed OS in this cohort compares favorably to OS reported in contemporary Phase 3 trials and might indicate a benefit of TARE with appropriate patient selection at experienced centers with dedicated MTB.
Relevance for Patients: Oncologists treating patients with CRLM should consider referral to a tertiary treatment center with a multidisciplinary team and TARE treatment expertise.

1. Introduction

The liver is the most common site of distant metastasis in colorectal carcinoma (CRC) with 50–70% of patients developing colorectal liver metastases (CRLM) during the disease [1]. Liver failure is the main cause of death in CRC patients. Standard of care treatment for CRLM includes curative intent resection and systemic therapy [1]. However, surgery is only applicable in 10–20% of cases, and of patients who undergo resection, long-term remission is only achieved in 20% of cases [1]. Over the past two decades, there have been some advances in systemic therapy; however, control of liver metastases remains an unmet need. Transarterial radioembolization (TARE) using yttrium-90 spheres (Y90) has been shown to induce tumor responses and delay progression of CRLM across all lines of treatment [2]. However, randomized trials in first and second-line CRLM patients failed to show an overall survival (OS) benefit in unselected populations [3,4]. There is also a concern that early exposure to internal liver radiation might lead to early and/or delayed radiation-induced damage which could compromise long-term outcomes of patients [5]. The objective

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of this work was to describe the survival of consecutive patients with CRLM treated with radioembolization (Y90 SIRspheres and Theraspheres) at a single academic institution.

2. Materials and Methods

The institutional review board approved a retrospective single-institution study. Consecutive patients with CRLM treated at least once with TARE between 01/2016 – 07/2020 were included in the analysis. The sample size was based on all available patients seen at the institution within the time frame. The start date for data collection was determined as the time when all involved investigators became part of the multidisciplinary tumor board at the institution. The end date for data collection was determined as 24 months before the data analysis, hence allowing for at least 24-month follow-up for patient survival. This retrospective chart review study was conducted at a tertiary referral center, and patients' records were reviewed using institutional electronic medical records. Clinically relevant variables including dates of diagnosis and death, demographics, genomic analysis, primary tumor location, chemotherapy regimen, laboratory values, and Eastern Cooperative Oncology Group (ECOG) performance status were extracted from patient charts. OS was calculated from the time of Stage 4 CRC diagnosis to death. Liver progression-free survival (LPFS) was calculated from the date of the first TARE procedure until the date of documented disease progression or death. Radiographic response was based on RECIST v1.1. Patients still alive at the time of last available follow-up were censored. We performed descriptive analyses for relevant patient and tumor characteristics, Wilcoxon Signed-Rank Test for comparison of continuous variables, and Kaplan–Meier estimates for survival.

The majority of mCRC patients were treated with resin and a few with glass Y90 microspheres according to previously published methodologies [6-8]. Specifically, all cases were discussed at a multidisciplinary tumor board consisting of hepatobiliary surgeons, medical oncologists, interventional and diagnostic radiologists, radiation oncologists, and clinical research personnel. Once deemed appropriate candidate for radioembolization (i.e., unresectable disease and liver limited/dominant metastases), patients underwent a mapping angiogram to determine tumor vascular supply, identify extra-hepatic arteries that require embolization to avoid iatrogenic gastrointestinal radiation ulcers, and determine the tumor and treatment volumes as well as the lung shunting fraction with MAA administration.

The microspheres type (resin vs. glass) and the treatment type (lobar or segmental) affected the method of Y90 activity calculation. Moreover, the method evolved during the study period. For resin microspheres, the body surface area (BSA) method was almost exclusively utilized. The activity to be administered to the target lobe was based upon:

Prescribed activity (GBq) = (BSA-0.2) + ([Tumor mass/Total liver mass] × 100)

If patients had received several lines of chemotherapy, the BSA prescribed activity was reduced empirically by up to 30% to reduce the risk of radiation-induced liver disease.

For glass microspheres, the medical internal radiation dose (MIRD) model was used:

Prescribed activity (GBq) = (Target dose [Gy] × Liver mass [kg])/(50 × [1–Lung shunting fraction] × ├ [1–Percent residual after infusion])

The liver volume was determined by computed tomography (CT), magnetic resonance imaging, or cone-beam CT. No adjustments were made for prior cytotoxic chemotherapy. For segmental treatments, the activity was derived from calculating the dose for the entire lobe even though given to selectively to a single segment [9-11].

Routine imaging after completion of TARE was performed at 8 weeks. A positron emission tomography scan was performed post-Y90 treatment to evaluate treatment.

3. Results

A total of $n = 55$ patients were included in the study. Follow-up time for survival in the entire cohort was at least 24 months. Patient demographics and tumor characteristics are shown in Table 1. Baseline and post-TARE liver function tests are shown in Table 2. Median time from diagnosis to first TARE was 16.4mo (1.7–95.6) (Figure 1A). Of note, 36.4% of the patients ($n = 20$) were treated within the first 12 months of diagnosis. Eleven patients (20%) were re-treated with TARE. Median OS from diagnosis and first TARE was 43.2 months (29.5–68.7) and 16.7 months (9.9–35.2), respectively.

Median LPFS was not reached (95% CI: 4.8 months to not evaluable) (Figure 1B). In 48 patients with at least one follow-up scan post-TARE, two patients had a complete response and 20 patients had a partial response, that is, overall response rate of 45.8%. The clinical benefit rate (i.e., stable disease or better) was 65.6% (31 of 48 patients).

4. Discussion

Surgical resection is recommended for patients with CRLM and associated with long-term survival in a subset of patients [12]. However, only 10–15% of patients with CRLM are candidates for curative intent liver resection. While initially effective, resistance to multi-agent systemic treatment will invariably develop in virtually all patients with CRLM. Progression-free survival (PFS) decreases with each subsequent line of systemic treatment [1].

To address the unmet need of control of liver metastases in CRLM, two randomized Phase III trials tried to address the role of TARE in first-line and second-line treatment of CRLM [3,4]. Both trials failed to show an actual OS benefit, despite of higher objective response rate and liver PFS in both trials. It is unclear why no survival benefit was seen in both trials despite improvement of other endpoints. While patient selection (e.g., performance status, disease volume, and extrahepatic disease) and trial design (timing of TARE, choice, and dose of systemic treatment) might have contributed to the results, there remains a concern that acute and delayed liver toxicity from TARE might negate any initial positive effect of tumor control in the liver.

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Table 1. Patient and tumor characteristics

Total patients, *N* (%)	**55 (100)**
Age at diagnosis, years	
Median	60
Range	36–84
Gender, *N* (%)	
Male	21 (38.2)
Female	34 (61.8)
Ethnicity, *N* (%)	
Caucasian	30 (54.5)
Hispanic	9 (16.4)
Asian	9 (16.4)
Other	7 (12.7)
ECOG performance status, *N* (%)	
0	18 (32.7)
1	32 (58.2)
2	5 (9.1)
Tumor sidedness, *N* (%)	
Left	40 (72.7)
Right	13 (23.6)
Unknown	2 (3.6)
Primary tumor resected, *N* (%)	
Yes	50 (90.9)
No	5 (9.1)
TARE, *N* (%)	
Unilobar	13 (23.6)
Bilobar	42 (76.4)
Re-treatment	8 (14.5)
MSI-high, *N* (%)	
Yes	2 (3.6)
No	32 (58.2)
Unknown	21 (38.2)
RAS/RAF mutation presence, *N* (%)	
Yes	19 (34.5)
No	27 (49.1)
Unknown	9 (16.4)
Number of prior systemic treatments before TARE, *N* (%)	
1	21 (38.2)
2	20 (36.4)
≥3	12 (21.8)
Unknown	2 (3.6)
Number of total systemic treatments, *N* (%)	
1	6 (10.9)
2	14 (25.5)
≥3	29 (52.7)
Unknown	6 (10.9)
Type of prior systemic treatments before TARE, *N* (%)	
FOLFIRI±biologic	10 (18.2)
FOLFOX/CapeOx±biologic	23 (41.8)
FOLFOXIRI±biologic	19 (34.5)
Other	2 (3.6)
Unknown	1 (1.8)

Abbreviations: FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; CapeOx: Capecitabine and oxaliplatin; FOLFOXIRI: Fluorouracil, leucovorin, irinotecan, and oxaliplatin

Table 2. Liver function parameters

	Baseline (range)	**Post-TARE (range)**	***P***
Alkaline phosphatase (U/mL)	112.0 (36.0–782.0)	198 (73–1442.0)	<0.001
Albumi*n* (g/dL)	4 (1.8–4.9)	3.55 (2.2–4.7)	<0.004
Bilirubi*n* (mg/dL)	0.5 (0.2–2.3)	0.8 (0.2–5.6)	<0.001
ALT (U/mL)	24 (8–149)	28.5 (9–173)	<0.004
AST (U/mL)	28.5 (13–100)	39.5 (12–121)	<0.001

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase

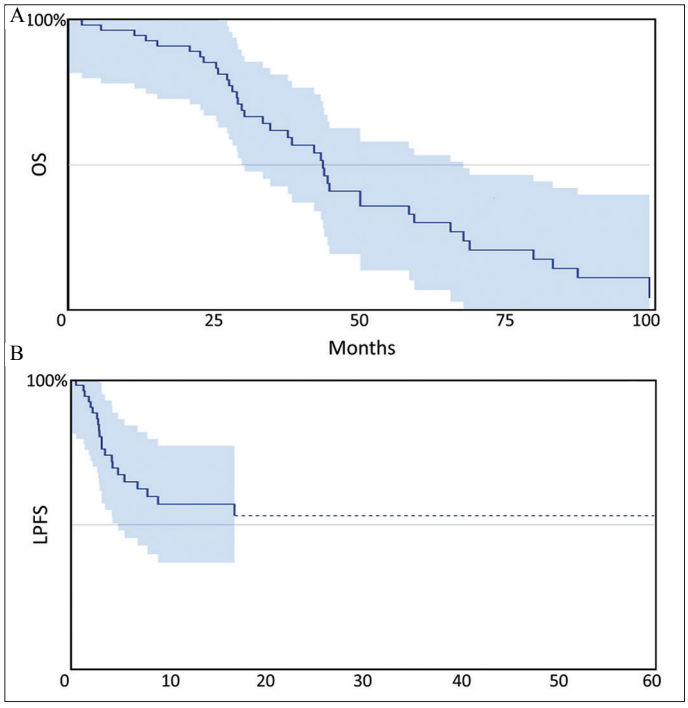

Figure 1. Overall survival of the population from the date of diagnosis (A) and liver progression-free survival from the date of first transarterial radioembolization (B). Blue area denotes the 95% confidence intervals.

The present study reports the outcome of a single-center consecutive cohort of CRLM patients treated with TARE. In this cohort of patients treated at an academic medical center with a multidisciplinary liver tumor board and experience in TARE, the mOS of more than 43 months does not appear to be diminished compared to results from contemporary mCRC trials with an estimated survival from initial diagnosis of stage IV mCRC of 30–40 months [13]. Importantly, more than a third of the patients were treated with TARE within 12 months of initial diagnosis with no observed detrimental longer-term effects. The minimum follow-up time was at least 24 months, hence long enough to show any potential delayed toxicity from early integration of TARE.

There are important differences between the design of the Sirflox trial in the first-line setting and the integration of TARE at our institution which might explain the favorable outcomes reported here. At our institution, patients with newly diagnosed CRLM are presented at the MDT. If the liver metastases are not deemed resectable initially, then patients are treated with full dose

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multiagent systemic treatment (two or three drug regimens) plus an appropriate biologic agent based on the tumors mutational status for 3–4 months. After this initial induction phase with reduction in the tumor burden, the patients are re-evaluated with repeat imaging at the MDT. If resectable, they will proceed at this stage with liver resection. However, patients deemed still unresectable by the MDT are evaluated for the absence of extrahepatic metastases, preserved performance status of ECOG 0-1, adequate kidney and liver function (including total bilirubin <2 mg/mL), and referred for TARE for consolidation. Maintenance single agent fluopyrmidine treatment is usually given before TARE and in between TARE treatments (i.e., both lobes of the liver, if indicated). The extent of TARE, dosing, and choice of spheres is based on the treating physician's discretion. After TARE, the patients continue maintenance chemotherapy, and about 2–3 months later are evaluated for response. At that time, those with further tumor response deemed resectable are referred for liver resection. In addition, if after about 6–8 months of treatment as outlined here the patients are in partial or complete remission, they are referred for resection of the primary tumor, hence rendering the patient disease-free.

Thus, the approach to incorporating TARE at our MDT is focused on appropriate patient selection which includes an intensive initial systemic tumor debulking and careful patient selection based on the clinical criteria above. This approach is very different from the Sirflox trial where patients were randomized to TARE within the first two cycles of chemotherapy and received suboptimal doses of systemic treatment during the first three cycles of systemic treatment. In addition, about a third of the patients had extrahepatic disease. Taken together, we believe these differences in patient selection and treatment might explain the survival outcomes in our cohort.

The main purpose was to focus on the major endpoint of OS, which can be objectively determined and hence is not biased by the frequency of scheduled diagnostic studies and their subjective interpretation. Furthermore, while there were no apparent differences in prognostic subgroups (e.g., by tumor sidedness; data not shown), it is important to note that due to relatively small numbers in each subgroup, the study did not have the power to detect potentially different outcomes based on clinical variables.

5. Conclusion

The herein presented data suggest that even relatively early integration of TARE in appropriately selected patients with CRLM who are reviewed by MDT and treated at an experienced academic center does not appear to negatively affect subsequent treatment or long-term outcomes.

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None.

Conflicts of Interest

FD reports honoraria from Astrazeneca, Eisai, Exelixis, Servier, Sirtex, and Ipsen. NAJ has received research funding to the institution from Sirtex and Theraspheres. All other authors declare no disclosures.

Ethics Approval and Consent to Participate

This work was performed under an IRB approved protocol at the University of California Irvine.

Consent for Publication

Due to retrospective nature of the study, this protocol was deemed IRB exempt for obtaining patient consents.

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CASE REPORT

Pancreas sparing duodenal resection in colorectal adenocarcinoma with local invasion to the duodenum: a case report and literature review

Si Ying Adelina Ho[1], Thomas Zheng Jie Teng[1,2]*, Vishal G. Shelat[1,2]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, [2]Department of General Surgery, Tan Tock Seng Hospital, Singapore

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**Corresponding authors*
Thomas Zheng Jie Teng
Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433 Singapore.
E-mail: zteng004@e.ntu.edu.sg

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ABSTRACT

Background: Pancreas sparing duodenal resection (PSDR) is commonly described in patients with familial duodenal adenomatous polyposis, duodenal gastrointestinal stromal tumors, duodenal trauma, or other primary duodenal lesions where the pancreas is not involved. PSDR in patients with metastatic involvement of the duodenum is rarely described. After reviewing the relevant literature, <5 PSDR for duodenal metastases reports were retrieved. Our patient was treated with PSDR for a local recurrence after a right hemicolectomy was performed for right colon adenocarcinoma a year before.
Aim: The aim of the study was to investigate if PSDR is feasible in this patient with recurrence of a locally advanced right colon adenocarcinoma invading the duodenum.
Case Summary: A 74-year-old female patient presented with the right iliac fossa pain and weight loss 1-year post-resection of the primary ascending colon cancer. A surveillance computed tomography scan of the thorax, abdomen, and pelvis showed a mass in the third segment of the duodenum. The decision to carry out a PSDR was made.
Results: The proximal and distal margins of the resected bowel were uninvolved by the invasive carcinoma and metastasis in five out of 12 regional lymph nodes was found. The post-operative course was complicated by a Grade B post-operative pancreatic fistula but recovered well post-drainage.
Conclusions: PSDR can be utilized in the management of duodenal metastases.
Relevance for Patients: PSDR can be performed in patients with duodenal metastases, offering a lower morbidity rate as compared to conventional pancreaticoduodenectomy.

1. Introduction

The pancreas is an unforgiving organ, and surgery involving the pancreas carries a significant risk of morbidity, especially for post-operative pancreatic fistulas (POPF). The incidence of POPF following distal pancreatectomy or pancreaticoduodenectomy is reported in up to 30% of patients [1]. Surgeons resort to centralizing pancreatic surgical services, technical modification of key surgical steps, standardized protocol-driven clinical care, and pharmacological intervention to reduce the morbidity following pancreatic resections [1,2]. One method of reducing morbidity would be to avoid pancreatic resections in, for example, duodenal-only lesions. This is especially relevant as POPF rates following pancreas resection are higher in patients with a soft pancreas texture and non-dilated pancreatic ducts, a typical feature of duodenal-only lesions [3,4]. Thus, pancreas-sparing duodenal resection (PSDR) is an attractive option, and it is no surprise that it is widely reported in patients with familial duodenal adenomatous polyposis, duodenal gastrointestinal stromal tumors, and a myriad of other primary duodenal lesions. Preserving the pancreas keeps the endocrine and exocrine function intact with a low risk of post-pancreatectomy diabetes and alleviates the

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need for pancreatic enzyme replacement therapy, with potentially improved quality of life following cancer survivorship [5]. Despite being accepted as a valid option in patients with selected pathologies, PSDR remains an uncommon surgical procedure.

Although PSDR is uncommon, it is one of the mainstream procedures for benign duodenal lesions and is widely commented on. Two broad classification systems describe PSDR – one related to duodenal resection (total or partial) and another related to the management of the ampulla of Vater (resection or preservation) [6,7]. Cantalejo-Díaz *et al.* performed a systematic review in 2019 and reported only 30 studies with 211 patients managed by PSDR with total duodenectomy [8]. In a single-center study over 14 years, Mitchell *et al.* reported that only 19 patients had underwent a PSDR with distal duodenectomy for various infra-papillary duodenal pathologies [9]. In a systematic review including 53 patients with locally advanced colon cancer invading the duodenum, Cirocchi *et al.* reported 14 patients managed by synchronous duodenal resection along with colectomy – ten with pedicled ileal flap duodenal reconstruction and four with direct suture repair of the duodenum [10]. As the majority of PSDR reports include primary duodenal pathologies or synchronous duodenal resection along with a colectomy for local duodenal invasion, PSDR in metastatic duodenal pathologies is rare [11-14]. We report a PSDR in a patient diagnosed with local recurrence of a right colon adenocarcinoma with the invasion of the duodenum following a right hemicolectomy performed a year before.

2. Case Presentation

A 74-year-old lady presented with the right iliac fossa pain, unintentional weight loss, and appetite loss on a background of hypertension and diabetes mellitus. She did not smoke nor consume alcohol and had no family history of colorectal cancer. Abdominal physical examination was unremarkable with no masses or organomegaly noted. A colonoscopy noted an ascending colon mass, and histology revealed a colonic adenocarcinoma. A staging computed tomography (CT) scan of the thorax, abdomen, and pelvis showed a 9 × 8 cm ascending colon mass involving the anterior abdominal wall and right adnexa with no distant metastases. Carcinoembryonic antigen was high at 160 μg/L (normal range: 0–2.5 μg/L). An open D2 right hemicolectomy was performed (Figure 1), and the final histology revealed pT4bN1bM0 colon adenocarcinoma with 2/27 positive lymph nodes. All the resection margins were free of the tumor, with the tumor invasion limited to Gerota's fascia. Capecitabine-based adjuvant chemotherapy was started.

A surveillance CT scan of the abdomen and pelvis done at 1 year showed a bulky necrotic tumor with an invasion of the third part of the duodenum (Figure 1 and 2). A magnetic resonance imaging scan of the pancreas confirmed duodenal invasion with the proximity of the tumor to the uncinate process or head of the pancreas (Figure 1). After a discussion with the multidisciplinary team, the decision was made for a PSDR.

The patient was counseled for multi-visceral resection, revision of ileocolic anastomosis, possible stoma creation, and a possible pancreaticoduodenectomy. Patient consented for the procedure and this case report was obtained. At exploratory laparotomy, the recurrence was noted to involve the second and third part of the duodenum and was close to, but not involving, the uncinate process of the pancreas. A PSDR was performed with excision of the recurrent tumor *en bloc*, including the ileocolic anastomosis, along with densely adherent small bowel loop and a cholecystectomy (Figure 1). The second and third parts of the duodenum up to the duodenojejunal flexure were resected, preserving the ampulla of Vater, pancreas, and uncinate process. Most of the small bowel was resected, leaving about 120 cm of the remnant small bowel. Reconstruction was performed by duodenojejunostomy at the junction of the first-second part of the duodenum and a new ileocolic anastomosis.

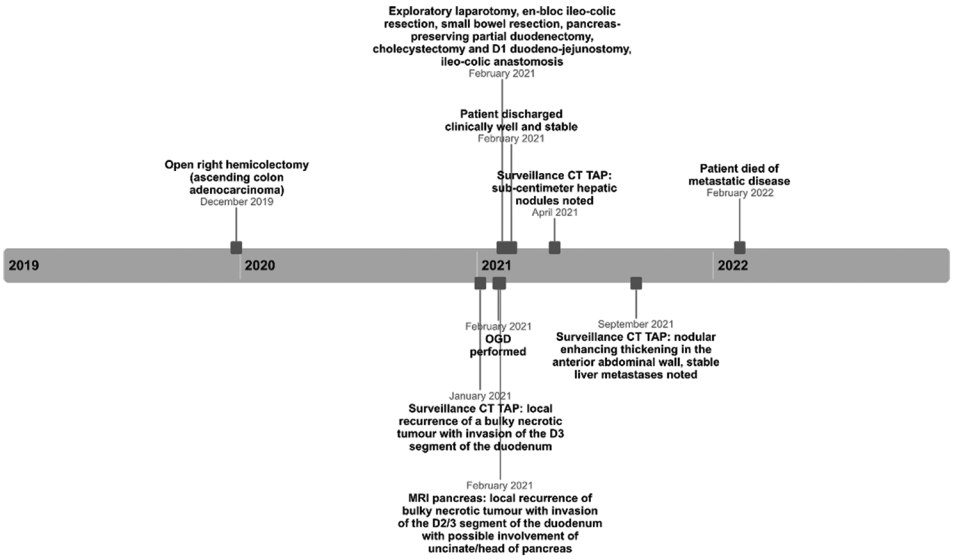

Figure 1. Timeline showing interventions performed on the patient.
Abbreviation: OGD: Oesophago-gastro-duodenoscopy

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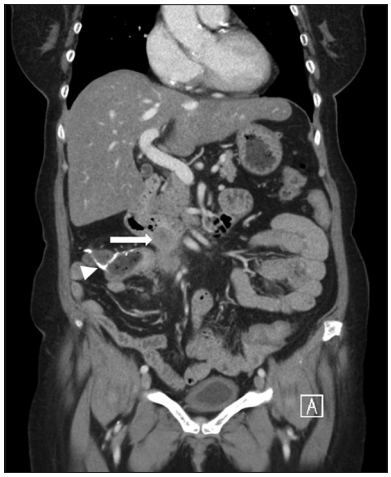

Figure 2. Surveillance computerized tomography scan of abdomen and pelvis showing the ileocolic anastomosis (white arrowhead) as well as a duodenal invasion (white arrows).

Histology revealed a moderately differentiated adenocarcinoma, suggestive of recurrence of the previously resected tumor, directly invading the duodenum. The proximal and distal margins of the ileocolic resection were uninvolved by the invasive carcinoma, and metastasis in five out of 12 regional lymph nodes was found. The postoperative course was complicated by a Grade B POPF according to the International Study Group of Pancreatic Surgery definition and this was managed with antibiotics and percutaneous image-guided drainage. The patient recovered well. However, a CT scan done at 3 months showed sub-centimetre hepatic lesions suspicious of metastases (Figure 1). Considering patient preferences for omitting intravenous chemotherapy, palliative oral capecitabine was commenced. She died of metastatic disease 28 months after the index surgery (Figure 1).

3. Discussion

PSDRs are uncommon procedures performed for benign, premalignant, or early-stage malignant duodenal lesions. For example, in patients with familial duodenal adenomatous polyposis, PSDR is done with prophylactic intent to reduce the risk of malignant transformation [11-16]. PSDR is anecdotally reported in malignant infiltration of the duodenum from other organs [6,14,15], or local invasion from colon cancer [10], and this is one of the first reports of PSDR for metastatic right colonic adenocarcinoma infiltrating into the duodenum.

PSDR is a technically challenging procedure, and it involves two considerations: Total or partial duodenal resection and management of the ampulla of Vater with its biliopancreatic digestive juices. With regards to the length of duodenal segment resection, Konishi *et al.* described four types of PSDR: (a) Pancreas-sparing total duodenectomy (complete resection of the duodenum, including pylorus), (b) pancreas-sparing subtotal duodenectomy (preserving the pylorus and duodenal bulb), (c) pancreas-sparing proximal duodenectomy (resection of the proximal duodenum), and (d) pancreas-sparing distal duodenectomy (resection of the distal duodenum) [6]. In our patient, pancreas-sparing distal duodenectomy was performed with transection at the level of the ampulla of Vater. With regards to the management of the ampulla of Vater, three types of technical modifications are described [7,17]. Type I includes the preservation of the pancreas's major and minor papilla and the upper or lower portion of the duodenal wall. Type II only preserves the major papilla anastomosed to the jejunum. Type III is an excision of the intraduodenal segment of the major papilla to expose the distal segments of the bile duct and pancreatic ducts before anastomosing them to the jejunum. In our patient, the Type I technique was sufficient for achieving oncological clearance [7,17].

PSDR saves the need for pancreaticoduodenectomies with a reduction in the risk of POPF. Preserving the pancreas allows for shorter surgical time, less intraoperative bleeding, and the omission of a hepaticojejunostomy in an undilated bile duct [8]. Pancreas-sparing procedures allow for the preservation of both endocrine and exocrine function of the pancreas with reduced risk of malabsorption and diabetes mellitus [8]. To note, PSDR is not always technically feasible, and all patients should be counseled for pancreaticoduodenectomy as the final decision rests on intraoperative assessment. In our patient, the uncinate process of the pancreas was in proximity but not directly involved, and thus, we managed to shave the tumor along with the pancreatic capsule, which contributed to a POPF. Cirocchi *et al.* have reported that multi-visceral resections, including synchronous duodenal resections, are safe and feasible in patients with locally advanced colon cancer and should be performed when R0 resection can be achieved [10]. Although the perioperative morbidity was comparable for patients with pancreaticoduodenectomies ($n = 39$) and duodenal resections ($n = 14$), the survival of patients with pancreaticoduodenectomies was superior when compared to local duodenal resection patients. Our patient had underwent duodenal resection for metastatic local recurrence and we decided to perform a PSDR rather than a pancreaticoduodenectomy as we were able to achieve R0 resection.

Although a pancreas-sparing procedure can achieve a lower morbidity rate compared to a standard pancreaticoduodenectomy [8], post-operative morbidity is still significant [18]. A PSDR leads to greater difficulty in reconstruction, with an increased risk of anastomotic leak and stenosis [19]. In a systematic review by Cantalejo *et al.* involving 211 patients, 49.7% of patients who underwent a pancreatic preserving duodenectomy had post-operative complications [8]. The most common complications reported were POPF (36.0%), delayed gastric emptying (15.7%), and wound infection (10.5%) [8]. Thus, even though the number of anastomoses is reduced in PSDR, the morbidity is comparable to a standard pancreaticoduodenectomy. Hence, PSDR is not performed with the intent of reducing post-operative morbidity, but instead to preserve pancreas function. If morbidity is reduced, it is a welcomed by-product. It is also important to consider nodal clearance in surgical decision-making and not only R0 resection. Thus, even though R0 clearance was achieved in most patients, survival after a pancreaticoduodenectomy was superior compared to duodenal resection in patients with locally advanced colon cancer [10].

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Another technical consideration would be to perform an ampullectomy alone. In a single-center study spanning over two decades and including patients with benign, premalignant, and early-stage malignant duodenal lesions, Papalampros *et al.* reported 10 patients with PSDR and 14 patients with transduodenal ampullectomies [20]. Although transduodenal ampullectomies were associated with a shorter operative time (145 min vs. 183 min, $P < 0.05$) and blood loss (85 vs. 125 ml, $P < 0.05$) compared to PSDR, overall morbidity was 54.2% [20]. Thus, it appears that morbidity is inherent in the procedure regardless of duodenal preserving approaches (such as ampullectomies) or PSDR. In our patient, the ampulla was not invaded by the malignant recurrence. Thus, the ampulla-preserving method was performed. Cho *et al.* reported treating a 50-year-old patient with duodenal invasion from an exophytic hepatocellular carcinoma with a PSDR involving a proximal duodenectomy [15]. They achieved negative resection margins with the proximal duodenectomy, and we achieved negative margins with a distal duodenectomy. Kimura *et al.* reported a 71-year-old female patient managed with a right nephrectomy for a retroperitoneal sarcoma presenting 3 years later with a recurrence infiltrating the hepatic flexure of the colon and second-third part of the duodenum [14]. The authors reported a PSDR involving a distal duodenectomy, like ours; however, they resected the ampulla and created a Type III reconstruction. The patient had a prolonged hospital stay of 67 days with various complications that did not require a relaparotomy, and no long-term outcome was reported. Overall, while PSDR shows promise as a potential surgical approach for duodenal metastases, its application should be carefully considered on a case-by-case basis, taking into account the patient's specific circumstances and the surgeon's expertise. Further studies and collaborative efforts are needed to expand our understanding of this procedure and optimize its outcomes.

4. Conclusion

PSDR in patients with metastatic colon cancer infiltrating the duodenum is safe and feasible. Pancreatic surgeons have a duty to share their experience to enhance understanding of the oncologic efficiency of this procedure in patients with primary or metastatic non-pancreatic malignancies.

Acknowledgments

None.

Conflicts of Interest

There are no commercial associations that might create a conflict of interest in connection with this manuscript.

Ethics Approval and Consent to Participate

Ethics approval and consent from patient were obtained.

Consent for Publication

Consent from patient has been obtained.

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ORIGINAL ARTICLE

Effectiveness of Pendleton's consultation model on the illness perception of heart failure patients

Hamideh Arab[1], Batool Tirgari[2]*, Atefeh Ahmadi[3], Roghayeh Mehdipour-Rabori[2], Yunes Jahani[4]

[1]Department of Medical Surgical Nursing, Razi faculty of Nursing and Midwifery, Kerman University of Medical sciences, Kerman, Iran, [2]Nursing Research Center, Kerman University of Medical Sciences, Kerman, Iran, [3]Department of counselling in midwifery, Razi faculty of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran, [4]Modelling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

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**Corresponding author:*
Batool Tirgari
Nursing Research Center, Kerman University of Medical sciences, Kerman, Iran.
Tel: +98 03431325219
Email: batool.tirgary@gmail.com

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ABSTRACT

Background and Aim: This study aimed to determine the effect of nursing consultation on the illness perception in heart failure patients.
Methods: In this experimental study, 100 heart failure patients were recruited through the convenience sampling method and were assigned to intervention and control groups by block randomization. In the first phase of the intervention, the researchers implemented Pendleton's consultation model. In the second phase, telephone follow-up was performed in four steps (1st, 2nd, 6th, and 12th weeks). The data were collected using a demographic information questionnaire and the illness perception questionnaire. Data were analyzed by SPSS 20 and using Chi-square, paired t, independent t, and covariance tests.
Results: There was no significant difference in demographic variables, and illness perception between the two groups before the intervention ($P > 0.05$).In the intervention group, the illness perception score increased from 31.33 ± 10.94 to 33.49 ± 10.25 after the intervention, which was not statistically significant ($P > 0.05$). Comparison between the two groups showed, in the intervention group the mean score of illness perception significantly improved after the intervention compared to the control group ($P = 0.003$).
Conclusion: The application of Pendleton's consultation model could improve the illness perception in heart failure patients.
Relevance for Patients: Considering that the cost of nursing consultations is not always low, it is suggested that nursing consultations be considered for patients with a higher number of sessions and telephone follow-ups for more efficacy if it is cost-effective.

1. Introduction

Heart failure is one of the most common cardiovascular disorders and is considered a chronic, progressive, and debilitating disorder [1]. It is the most common cause of hospitalization for patients over the age of 65. The heart failure rate of referrals to emergency departments and frequent hospitalizations is still high [2]. Heart failure is the most frequent reason for readmission within 30 days of discharge [3].

According to the latest reports, nearly six million people in the United States have heart failure. More than 550,000 new cases are diagnosed each year [2]. Heart failure affects 1–2% of the population or about 50 million people across Europe [4,5]. In Iran, the incidence of heart failure will increase to 3500 cases per 100,000 individuals in the future, and cardiovascular disorders such as heart failure are among the major causes of patient mortality and morbidity [6].

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Heart failure causes severe and progressive fatigue, intolerance to exercise, fluid retention, and dyspnea, which often result in reduced quality of life [7]. Research in neurocardiology has alluded to the presence of a "heart-brain" connection and the increased prevalence of anxiety, depressive, and stress symptoms among this patient population [8].

Seyam *et al.* [2013] concluded that it is necessary to provide appropriate consultation and special attention should also be paid to patients who have been hospitalized more often due to heart disease, as well as to those who have had a long history of heart disease. This ultimately prevents the recurrence of the disease and is useful in improving the quality of life and health [9].

Patient perception of the illness affects disease management and the psychological management of the patient. Being able to diagnose the cause of the disease helps patients to guide the disease control practical programs. The perception of the illness is the patients' organized cognitive reflection of their illness. According to the theory of Leventhal *et al.*, patients regulate their emotional behavior and response to the disease based on their perceptions of the nature, causes, consequences, control, and treatability of the disease [10]. Patient support aims at increasing the perception of individual control, which is one of the important components of illness perception. Patient support can be a primary care strategy in rebuilding health-facilitating programs, reducing fatigue, and improving quality of life. Therefore, having a complete understanding of the components of illness perception is useful and effective for guiding a person to a good quality of life [11].

Lucas *et al.* (2015) examined the effect of nurse consultation on heart disease, the beliefs, and the quality of life of heart failure patients. They found that being in touch with a nurse who specializes in heart failure patients, could improve patients' satisfaction with treatment decisions. However, it had less effect on a patient's beliefs compared to personal control and treatment control [4].

A study by Kadda *et al.* (2012) in Greece focused on the role of nursing education after a heart attack. The findings showed that nursing education regarding cardiac rehabilitation could improve health outcomes and reduce the risk of heart disease. A health education program organized by nurses for patients after a heart attack or surgery improves patients' knowledge of the disease and awareness of behavioral changes to prevent a new condition or hospital admission [12].

Lucas (2015) studied the effect of heart failure nurse consultations on patients' illness beliefs, mood, and quality of life over 6 months. The results showed that nursing consultation affected the belief in illness, satisfaction, and treatment decisions [4].

Given the increasing number of heart failure patients and its devastating effects on quality of life, it is recommended that nurses look for a new way to improve the quality of life of heart failure patients [1]. One of the nursing interventions is consultation [13]. Nurses play a key role in treatment because they are close to patients and their families throughout the disease process. Nurses need to meet the needs of patient care through training, consultation, support, supervision, and reinforcement. Nursing training in cardiac rehabilitation can improve health outcomes, and reduce the risk of heart disease. A health education program developed by nurses for patients improves patients' knowledge of the disease and awareness of behavioral changes to prevent a new event or hospital admission [12].

Results of previous studies showed that illness perception plays a predictive role in psychological and physical health conditions. Furthermore, these studies suggested that to understand the increase in adherence to therapy, the perception of the disease should be increased through education to patients. Thus, health-care providers should take interventions focused on changing illness perception to improve health outcomes in patients with heart failure [14-16]. As far as the authors are concerned, no study has focused on this issue in Iran. Therefore, the present study was conducted to determine the effect of nursing consultation on illness perception in heart failure patients.

2. Methods

2.1. Study design

The present study is an experimental study in which two groups of heart failure patients were assessed pre-and post-intervention.

2.2. Participants

In this study, 100 heart failure patients were selected by convenient sampling method and then divided into the intervention and control groups by block randomization method. In the block randomization method, the number of patients assigned to each group is almost equal. In this method, blocks were formed based on the variables considered in the present study. One-half of each block comprised intervention subjects and the other half includes the control group participants. The main goal of this method is to give a balance to the number of participants in each group.

The sample size was determined based on previous studies [17] and using the comparison formula of two averages and considering the following:

$$n = \frac{2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^z \sigma^2}{d^2}$$

d = 0.15, β = 0.80 α = 0.05

There were 50 patients in each group. Eventually, 100 participants entered the study. The study was able to detect at least a 15% of difference in the illness perception between the two groups, with a power of 80%. By performing power analysis using our data, the power value of 0.89 was obtained, which is very good and acceptable and even higher than 0.80 that we used to calculate the sample size.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: A minimum of 18 years and a maximum of 80 years, a history of chronic heart failure based on clinical signs, electrocardiography, and echocardiography, indicating an ejection fraction of <40% based on the patient's profile and with the approval of a cardiologist. The patients had to be in Classes 2 and 3 heart failure, according to the New York Heart Association's

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classification system and it had to be approved by two cardiovascular specialists. In addition, the patient had to be able to complete the questionnaire. The exclusion criteria included severe mental or cognitive impairment, pregnancy, and lactation. The patients who were fully aware of their care (medical staff, participation in related training courses) were removed from the experiment. The other exclusion criteria were participation in a similar research project, malignancy, experiencing severe psychological distress after entering the study, the reluctance to continue participating in the research project, and death during the study.

2.4. Intervention and data collection

Patients with chronic heart failure, whose disease has been proven and were under treatment by a cardiologist in the CCU and cardiac wards in the hospitals affiliated with the Kerman University of medical sciences, were divided into intervention and control groups. Initially, the purpose of the study was explained to the subjects. Written consent was obtained from those who were registered. The questionnaires (demographic information and illness perception) were completed by both groups.

We tried the intervention consistently applied among nurses and patients. Therefore, the first author administered the intervention to all patients. For the homogeneity of the sample, the patients were selected based on the inclusion criteria and were homogenized between the two groups.

For the intervention group, the intervention was performed in two phases. The first phase was based on Pendleton's consultation model and the second phase was by telephone follow-up. Pendleton's consultation was given face-to-face and individually, in two 15-min hospital sessions. Pendleton's consultation model was developed by Pendleton *et al.* in 1984. It is a patient-centered model based on seven tasks [18].

The information given to individuals in the form of the Pendleton model in this study is divided into five general areas. To provide all the steps, time and resource constraints were considered for the patients and the consulting nurses:

(1) To define the reason for the patient's attendance, including:
   a. The nature and history of the heart failure problem in the patient
   b. Their etiology
   c. Patients' ideas, concerns, and expectations about heart failure when hospitalized and when living with this disease at home
   d. The effects of the mental and physical problems, and the life quality in general
(2) To consider other problems of the patient:
   a. Other diseases and problems
   b. At-risk factors of the issues mentioned in section (a)
(3) With the patient, to choose an appropriate action for each problem.
(4) To achieve a shared understanding of the problems with the patient.
(5) To involve the patients in the management and encourage them to accept appropriate responsibility [13].

It should be noted that the first consultation session was given immediately after the patient's condition was stabilized and the symptoms improved. It was done in the ward and a quiet room such as the examination room, and it lasted for 15 min. The second session was held the next day for 15 min.

In the second phase, the second researcher also performed the telephone follow-up in four stages (1st week, 2nd week, 6th week, and 12th week). Phone follow-up is intended to further communicate with the patient in a supportive and motivational environment. The time was set at a maximum of 5 minutes. The required explanations and guidelines were given to the patient. The control group also received the ward routine care. After the intervention and at the end of the 12th week, both groups completed the illness perception questionnaire (IPQ). The patients were selected from different hospitals to prevent the contamination of the intervention and control groups. Two faculty members who are members of the research team and one non-faculty member of the research team determined the validity and the content of the consultations. The researchers advised everyone precisely according to the protocol, thus the conditions were the same for all patients.

2.5. Instruments

The demographic questionnaire and the IPQ were used for data collection.

The demographic questionnaire included questions about age, gender, employment status, disease class, economic and lifestyle level, and comorbidity.

The IPQ has nine subscales and designed by Brad Benet *et al.* (2006). Each subscale is a question that best summarizes the IPQ-R of the material on each subscale. Each rating scale is answered from 0 to 10. Each subscale measures a component of illness perception. Five subscales measure the cognitive response to disease, including (1) perception of consequences, (2) duration of illness, (3) personal control, (4) treatability, and (5) recognizing symptoms. There are two emotional responses: Concern about illness and emotions. One measures the ability to perceive and understand the disease. Open-ended questions are used. The score is given from 0 to 100. Zero indicates the lowest level of perception, and 100 indicates the highest level of perception [19,20]. Bagherian *et al.* (2008) prepared the Persian version of this questionnaire. Alpha Cronbach's Persian version was 0.84, and its correlation coefficient with the Persian version was 0.71 [20].

2.6. Data analysis

SPSS software version 20 was used to analyze the data. To assess homogeneity between the groups, an independent t-test and Chi-square test were used. To compare the pre- and post-intervention perception of the illness paired t-test was used. T-test was used to compare the mean score of illness perception between the two groups. To control the varying effect of the perception of the illness before the intervention, a covariance test was used to evaluate the changes after the intervention. The significance level was considered to be 0.05.

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Table 1. Demographic characteristics of patients with heart failure

Variable	Control group		Intervention group		Chi-square	*P*
	Frequency	Percentage	Frequency	Percentage		
Gender						
Female	25	55/6	23	51.1	0.179	0.673
Male	20	44.4	22	48.9		
Education						
Illiterate	14	31.1	20	44.4	4.772	0.311
Below diploma	16	35.6	18	40.0		
Diploma	7	15.6	4	8.9		
Associate degree	7	15.6	2	4.4		
Bachelors' degree	1	2.2	1	2.2		
Marital Status						
Single	3	6.7	8	17.8	2.589	0.108
Married	42	93.3	37	82.2		
Spouse's education						
Illiterate	17	39.5	19	48.7	3.682	0.451
Below diploma	19	44.2	16	41		
Diploma	5	11.6	3	7.7		
Associate degree	2	4.7	0	0.0		
Bachelors' degree	0	0.0	1	2.6		
Employment status						
Housewife/stay-at-home dad	17	37.8	19	42.2	5.318	0.256
Employee	4	8.9	0	0.0		
Student	11	24.4	13	28.9		
Business	13	28.9	12	26.7		
Retired	0	0.0	1	2.2		
Spouse's employment status						
Housewife/stay-at-home dad	1	45.2	19	55.9	1.504	0.681
Employee	1	2.4	0	0.0		
Student	0	0.0	0	0.0		
Business	12	28.6	8	23.5		
Retired	10	23.8	7	20.6		
Lifestyle						
With family	4	8.9	8	17.8	1.609	0.657
With spouse	31	68.9	27	60.0		
With children	6	13.3	6	13.3		
Alone	4	8.9	4	8.9		
Income						
Low	20	44.4	16	35.6	1.524	0.476
Average	24	53.3	26	57.8		
High	1	3.3	3	6.7		
Physical illness						
Yes	31	75.6	32	71.1	0.222	0.638
No	10	28.9	13	28.9		
Illness type						
Lower extremity swelling	10	43.5	2	14.3	5.89	0.117
Respiratory disease	8	34.8	6	42.9		
Diabetes	5	21.7	4	28.6		
Renal disease	0	0.0	2	14.3		

(*Contd...*)

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Table 1. (*Continued*)

Variable	Control group		Intervention group		Chi-square	*P*
	Frequency	Percentage	Frequency	Percentage		
Duration of heart disease						
<1 year	7	15.6	11	24.4	5.561	0.135
Between one and three years	11	24.4	10	22.2		
3–5 years	17	37.8	8	17.8		
More than 5 years	10	22.2	16	35.6		
Hospitalization history						
1–2	9	20.0	12	26.7	5.821	0.121
3–4	12	26.7	14	31.1		
5–6	17	42.2	9	20.0		
7 and more	5	11.1	10	22.2		
Tobacco use						
No	18	40.0	27	60.0	5.227	0.265
Opium	10	22.2	6	13.3		
Cigar	5	11.1	4	8.9		
Meth	0	0.0	1	2.2		
Opium and cigar	12	26.7	7	15.6		
Ejection fraction percentage						
10–20%	8	17.8	11	24.4	1.068	0.586
20–30%	21	46.7	22	48.9		
30–40%	16	35.6	12	26.7		
Heart failure Class						
Class 2	16	35.6	15	33.3	0.049	0.824
Class 3	29	46.4	30	66.7		

2.7. Ethical considerations

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1397.431, 29-1-2019). The purpose of the research was explained to the samples. The participants were not obliged to participate in the study. The letter of recommendation was obtained from the Faculty of Nursing and presented to the research environment authorities before collecting the data. Written consent was obtained from the study participants before they took part in the study. The consultation was given to the control group patients after completing the study upon their demand.

3. Results

3.1. Demographic characteristics

According to Table 1, most of the samples were in the following groups: Female (55.6%), below diploma (35.6%), and married (93.3%). There was no statistically significant difference between intervention and control groups in terms of demographic and clinical characteristics ($P > 0.05$).

The mean age of the control group was 59.96 and the mean age of the intervention group was 60.09. There was no statistically significant difference between the mean age of the two groups ($P > 0.05$).

3.2. Illness perception

According to the results of the t-test, there is no significant difference between mean scores of illness perception pre-intervention between the two groups ($P > 0.05$) (Table 2), whereas a post-intervention comparison showed a significant difference between the two groups ($P < 0.005$). To control the varying effect of the perception of the illness before the intervention, a covariance test was used to evaluate the changes after the intervention. As shown in Table 3, the mean score of illness perception after the intervention (by controlling the previous score) in the intervention group is 5.53 points higher than the control group, which is a statistically significant difference (Table 3).

Table 2. Comparing mean score for illness perception before intervention between two groups

Group	Mean±SD	Statistic	*P*-value
Control	4.98±28.22	1.73	0.087
Intervention	10.94±31.33		

Table 3. Comparing mean score for illness perception after intervention between two groups using analysis of covariance

Group	Mean±SD	Mean difference (95% confidence interval)	Statistic	*P*-value
Control	7.65±27.47	5.53 (1.69, 9.36)	8.23	0.005
Intervention	10.25±33.49			

According to the results of the paired *t*-test, there was no significant difference in the mean scores of illness perception in the control group before and after intervention ($P > 0.05$). In the

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Table 4. Pre- and post-intervention mean score for illness perception in patients with heart failure

Variable	Intervention	Control group				Intervention group			
		Mean	SD	Paired *t*-test	*P*	Mean	SD	Paired *t*-test	*P*
Illness perception	Pre-test	28.22	4.98	0.670	0.50	31.33	10.94	−-014	0.31
	Post-test	27.47	7.65			33.49	10.25		

intervention group, the mean score of illness perception increased from 31.33 before the intervention to 33.49 after the intervention, but this improvement was not statistically significant ($P > 0.05$) (Table 4).

4. Discussion

The results of this study indicated that Pendleton's consultation model improved the illness perception in patients with heart failure. These findings are consistent with previous studies.

Rakhshan (2013) conducted a study entitled the perception and experience of patients with pacemakers from the disease process: Based on Leventhal's model. They assessed 51 patients with a pacemaker over 10 weeks. Their findings suggest that patients with pacemakers expect less severity from their illness after the consultation-training intervention. They also consider their disease as a chronic, controllable, and treatable disease. They are more adaptable to the disease and more aware of the positive cognitive and emotional manifestations of their illness. This means that they have a more favorable interpretation of their disease and its conditions [21]. In another similar study, Tabarian *et al.* (2016) examined the effect of consultation and training on illness perception based on Leventhal's self-regulatory model. The results showed that after the intervention, the two groups had a statistically significant difference in the overall mean score of the illness perception. It was determined that the mean score of the illness perception and its components in the intervention group increased [22].

Petrie *et al.* (2012) in a clinical trial examined the effect of a text message program on adherence to the treatment regimen for young patients with asthma in New Zealand. The purpose of this program was to change the perception of the illness and the patient's beliefs about medication. The researchers reported that the text message program increased the rate of adherence to asthma prevention drugs and may be useful in other diseases where adherence to the treatment is important [23]. Jahandar *et al.* (2016) examined the effectiveness of cognitive-behavioral intervention on illness perception and quality of life of Type 2 diabetic patients. The results showed that relatively short-term cognitive-behavioral group intervention could lead to a significant increase in illness perception in Type 2 diabetic patients [24].

Perception of the illness affects how a patient controls the disease, and adapts to it. Health interventions through consultation and education based on the perception of the illness can help improve the health and recovery of the patient. Patients follow consultation to manage their illness when they have a clear understanding of their illness. A correct understanding of health can reduce mortality, complications, and disease outcomes.

Therefore, it is safe to say that although it is useful for patients to provide consultation to them during hospitalization, especially in chronic diseases, this does not merely suffice. It should also last after discharge. Furthermore, care managers in the primary clinical setting could create the conditions not only for a better control of the disease, but also for the prevention of adverse events in patients with chronic cardiovascular disease such as heart failure [25]. As a result, coordinating regular consultations based on the needs of patients at any time is vital in controlling and preventing heart failure. It may also raise the quality of life in these patients.

There was an average level of cooperation from some patients in completing the questionnaire. By explaining the objectives of the research and reassuring patients that the information was confidential, we were able to collect the data. Data are based on self-reports. This is a limitation. Given that the CCU ward of Shahid Bahonar Hospital was dissolved during the collection of research data, we were not able to collect the data of patients assigned to this hospital, thus patients from two other hospitals replaced them. This was another limitation of this study.

5. Conclusion

The findings of this investigation revealed that Pendleton's consultation model improved the illness perception in patients with heart failure. Thus, all medical staff should devote their clinical interventions and special measures to increasing the illness perception in these patients. They also need to consider training and consultation as the benchmark of their efforts. It is important to note that the effectiveness of the Pendleton model or any consultation model can vary depending on factors such as the context of care, health-care professional training, patient population, and individual preferences. Therefore, future studies with a focus on the aforementioned variables are required. Furthermore, it is also suggested that in future studies, the nursing consultation needs to be done with a higher number of sessions and telephone follow-ups for more efficacy, if it is cost-effective.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1397.431, 29-1-2019). The purpose of the research was explained to the samples. The participants were not obliged to participate in the study. The letter of recommendation was obtained from the Faculty of Nursing and presented to the research environment authorities before collecting the data. Written consent was obtained from the study participants before they took part in the study. The consultation was given to the control group patients after completing the study on their demand.

Consent for Publication

Not applicable.

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ORIGINAL ARTICLE

Changes in correlations between cervical and distal spinal sagittal alignments in asymptomatic population with aging

Jiang Xu[1,2], Junlong Zhong[2], Zongmiao Wan[2], Jiachao Xiong[2], Zhenhai Zhou[2], Honggui Yu[2], Kai Cao[1,2*]

[1]Nanchang University Spine and Spinal Cord Institute, The First Affiliated Hospital of Nanchang University, Nanchang, 330006, China, [2]Department of Orthopedics, The First Affiliated Hospital of Nanchang University, Nanchang, 330006, China

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**Corresponding author:*
Kai Cao
The Orthopedic Hospital, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi Province, 330209, China.
E-mail: kaichaw@126.com

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ABSTRACT

Background: In recent years, the correlations between spinal sequences and aging have been identified. However, the trends in correlations between cervical and distal spinal alignments with aging in asymptomatic populations remain underexplored.

Aim: This study aimed to compare the correlations between cervical and distal spinal sagittal alignments in different age groups as well as investigate their trends during the aging process in an asymptomatic population.

Methods: A total of 128 asymptomatic healthy volunteers were enrolled and stratified into four groups according to age (Group A: ≤20 years; Group B: 21 – 40 years; Group C: 41 – 60 years; Group D: >61 years), with 32 subjects in each group. Then, sagittal spinal parameters including C0-1 Cobb angle (C0-1 CA), C1-2 Cobb angle (C1-2 CA), C0-2 Cobb angle (C0-2 CA), C2-7 Cobb angle (C2-7 CA), C2-7 sagittal vertical axis (C2-7 SVA), neck tilt, thoracic inlet angle (TIA), T1 slope (TS), thoracic kyphosis (TK), lumbar lordosis, pelvic tilt, sacral slope, pelvic incidence, and C7-S1 sagittal vertical axis (C7-S1 SVA) were measured, and differences in parameters among the four groups were analyzed. Finally, the trends in correlations between the cervical and distal spinal sagittal parameters were investigated in the different age groups.

Results: No significant correlations were detected between upper cervical sagittal parameters (C0-1 CA, C1-2 CA, and C0-2 CA) and distal spinal sagittal parameters in the four groups. An increasing trend with aging was discovered in the correlations between subaxial cervical sagittal parameters and distal spinal sagittal parameters. Finally, significant correlations were observed between TS and TK, as well as between TIA and TK in the four groups.

Conclusions: Subaxial cervical alignments exhibit a close correlation with distal spinal alignments during the aging process in the asymptomatic population. An increasing trend was observed with age in the correlations between C2-7 CA, C2-7 SVA, and distal spinal sagittal parameters.

Relevance for Patients: Given the correlations between the cervical and distal spinal alignments, which tend to increase with age, it is crucial to pay special attention to the influence of C2-7 CA and C2-7 SVA on distal spinal alignments before spinal surgery for patients.

1. Introduction

The sagittal balance of the spine has recently garnered increasing attention from spinal surgeons [1,2]. Indeed, sagittal alignment of the spine provides key information about spinal function and largely influences spinal biomechanics. Thus, maintaining the sagittal balance of the spine plays a vital role in maintaining the normal posture of the body [3].

As is well documented, the spine is composed of cervical and distal segments. As an essential component of the spine, the cervical spine plays an instrumental role in maintaining the

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sagittal balance of the spine and the head position [4]. Meanwhile, a compensatory interaction has been reported between cervical alignment and distal thoracic, lumbar, and pelvic alignment to maintain the sagittal balance of the spine [5,6]. There is evidently a close relationship between cervical and distal spinal alignments.

Moreover, our previous study revealed fluctuations in cervical alignment parameters with aging in asymptomatic populations [7]. Nevertheless, the correlation between cervical alignment and distal spinal alignment with aging remains elusive. Therefore, the purpose of this study was to investigate trends in the correlations between cervical and distal spinal sagittal alignments in the asymptomatic population with aging.

2. Materials and Methods

2.1. Selection of subjects

This study was approved by the Institutional Review Board of the institute. A total of 206 volunteers consented to participate in the study from September 2020 to December 2021, and written informed consent was obtained from each volunteer. The inclusion criteria of the asymptomatic population were as follows: (1) no past history of chronic neck, low back, and back pain; (2) no history of spinal disease; (3) no history of hip, pelvic, or lower limb disease. The subjects were divided into 4 groups according to their age (Group A: ≤20 years old; Group B: 21 – 40 years old; Group C: 41 – 60 years old; Group D: ≥61 years old). Each group comprised 32 subjects. The age and body mass index of subjects were recorded.

2.2. Radiographic parameters

The subjects were placed in the upright position with a clenched fist resting on the supraclavicular fossa. Next, standard full-length anteroposterior and lateral radiographs of the spine were taken. The sagittal parameters of the global spine consisted of C0-1 Cobb angle (C0-1 CA), C1-2 Cobb angle (C1-2 CA), C0-2 Cobb angle (C0-2 CA), C2-7 Cobb angle (C2-7 CA), C2-7 sagittal vertical axis (C2-7 SVA), neck tilt (NT), T1 slope (TS), thoracic inlet angle (TIA), thoracic kyphosis (TK), lumbar lordosis (LL), sacral slope (SS), pelvic tilt angle (PT), pelvic incidence angle (PI), and C7-S1 SVA.

The aforementioned parameters were measured as follows: C0-1 Cobb angle was defined as the angle between McGregor's line (A) and the line (B) linking the anteroinferior and posteroinferior arch of atlas; C1-2 Cobb angle represented the angle between the line (B) linking the anteroinferior and posteroinferior arch of atlas and the parallel line (C) of the C2 lower end plate; C0-2 Cobb angle was the angle between the McGregor line (A) and the parallel line (C) of the C2 lower end plate; C2-7 Cobb angle was defined as the angle between the parallel line (C) of the C2 lower end plate and the parallel line (D) of the C7 lower end plate; C2-7 SVA characterized the distance between the vertical line from the center of C2 and the posterior superior corner of C7; NT symbolized the angle between two lines both originating from the upper end of the sternum, one of them being a vertical line, while the other one was connected to the center of the T1 upper end plate; TS was the angle between the horizontal plane and the parallel line of the T1 upper end plate; TIA was the angle between the line perpendicular to the T1 upper end plate and a straight line from the center of the T1 upper end plate to the upper end of the sternum; TK denoted the angle between the T1 upper end plate and the T12 lower end plate; LL represented the angle between the L1 upper end plate and the S1 upper end plate; SS was the angle between the sacral end plate and the horizontal plane; PT was the angle formed by the vertical line and the line passing through the midpoint of the sacral end plate to the center of the femoral head; PI was the angle between the line perpendicular to the midpoint of the sacral end plate and the line connecting the midpoint of the sacral end plate to the center of the femoral head; C7-S1 SVA was the distance between a vertical line from the center of C7 and the posterior corner of the sacrum. Examples of the above parameters are illustrated in Figure 1.

2.3. Statistical analysis

SPSS 22.0 statistical software (SPSS, Inc., Chicago, IL, USA) was employed for statistical analysis. One-way ANOVA statistical method was used for intergroup comparisons, and Pearson correlation analysis was used to analyze the correlation between cervical alignment and distal spinal alignment. All values were expressed as mean ± standard deviation, and a $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Demographic characteristics of asymptomatic volunteers

The study included 128 subjects, ranging in age from 16 to 81 years old and comprising 65 males and 63 females. The mean age of the subjects was 40.8 ± 20.0 years. The demographic data of volunteers are detailed in Table 1.

3.2. Parameters analysis

One-way ANOVA was utilized to analyze differences in global spinal sagittal parameters among the groups. The results revealed no significant differences in C0-1 CA ($P = 0.096$) and PI ($P = 0.502$) in the four groups. Meanwhile, there were significant differences in C1-2 CA ($P = 0.025$), C0-2 CA ($P = 0.050$), C2-7 CA ($P = 0.000$), C2-7 SVA ($P = 0.018$), NT ($P = 0.000$), TS ($P = 0.000$), TIA ($P = 0.000$), TK ($P = 0.000$), LL ($P = 0.007$), SS ($P = 0.019$), PT ($P = 0.000$), and C7-S1 SVA ($P = 0.000$) in the four groups. Details are summarized in Table 2.

The Pearson correlation coefficients of C0-1 CA, C1-2 CA, and C0-2 CA and distal spinal parameters were all lower than 0.3, and no apparent trend in correlation was observed with aging. In the four groups, the Pearson correlation coefficients between C2-7 CA and TK were -0.236 ($P = 0.193$), −0.362 ($P = 0.042$), −0.502 ($P = 0.003$), and −0.655 ($P = 0.000$), the coefficients between C2-7 SVA and SS were 0.045 ($P = 0.808$), 0.265 ($P = 0.143$), 0.362 ($P = 0.042$), and 0.628 ($P = 0.000$), while the Pearson correlation coefficients between C2-7 SVA and C7-S1 SVA were 0.213 ($P = 0.242$), 0.322 ($P = 0.072$), 0.460 ($P = 0.008$), and

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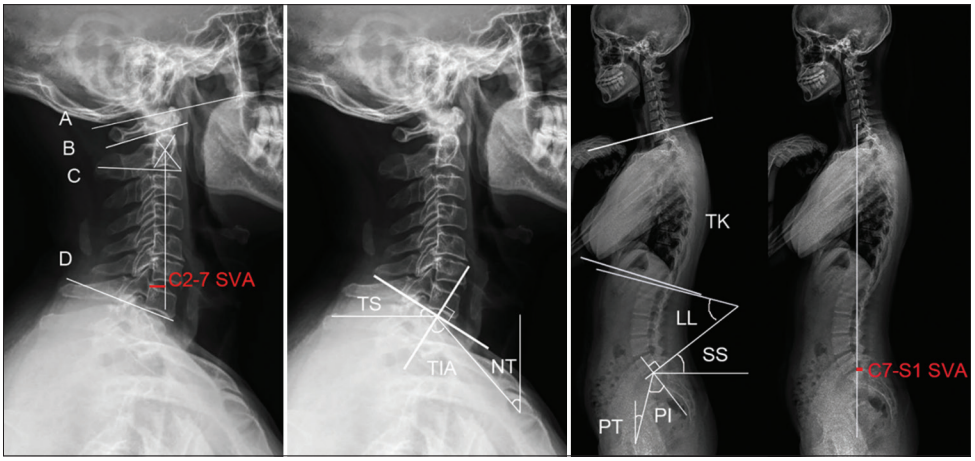

Figure 1. Illustrative schematic displaying cervical and distal spinal sagittal parameters: C0-1 CA, C1-2 CA, C0-2 CA, C2-7 CA, and C2-7 SVA, NT, TS, TIA, TK, LL, SS, PT, PI, and C7-S1 SVA.
Abbreviations: C0-1 CA: C0-1 Cobb angle; C1-2 CA: C1-2 Cobb angle; C0-2 CA: C0-2 Cobb angle; C2-7 CA: C2-7 Cobb angle; C2-7 SVA: C2-7 sagittal vertical axis; NT: Neck tilt; TS: T1 slope; TIA: Thoracic inlet angle; TK: Thoracic kyphosis; LL: Lumbar lordosis; SS: Sacral slope; PT: Pelvic tilt; PI: Pelvic incidence; C7-S1 SVA: C7-S1 sagittal vertical axis.

Table 1. Demographic data of the four groups

Characteristic	Group A: ≤20 years *N*=32	Group B: 21 – 40 years *N*=32	Group C: 41 – 60 years *N*=32	Group D: ≥61 years *N*=32
Male	18	17	13	17
Female	14	15	19	15
BMI (kg/m^2)	17.7±1.4	23.6±6.6	26.9±5.5	26.8±6.6
Age (years)	14.0±4.4	34.1±5.5	48.7±4.8	66.5±5.4

BMI: Body mass index

Table 2. Values of spinal sagittal alignment parameters in the four groups

Radiographic parameter	Group A: ≤20 years *N*=32	Group B: 21 – 40 years *N*=32	Group C: 41 – 60 years *N*=32	Group D: ≥61 years *N*=32	*P*-value
C0-1 CA	12.5±6.9	9.3±10.8	13.5±4.6	13.5±7.4	0.096
C1-2 CA	−20.4±5.6	−20.7±10.2	−24.0±5.9	−24.8±5.8	0.025*
C0-2 CA	−7.1±6.1	−11.5±8.4	−10.5±6.2	−11.3±7.2	0.050*
C2-7 CA	−7.9±8.2	−6.5±10.3	−13.1±8.0	−17.0±10.1	0.000**
C2-7 SVA	20.1±9.1	18.2±10.6	20.3±8.2	25.7±10.9	0.018*
NT	41.4±6.9	47.3±9.7	50.5±8.8	51.1±10.6	0.000**
TS	22.1±5.1	20.3±5.7	23.8±4.9	27.1±8.8	0.000**
TIA	63.5±9.8	67.6±9.5	74.2±8.3	78.2±11.8	0.000**
TK	36.0±7.2	38.6±8.1	42.5±7.7	48.3±10.9	0.000**
LL	−50.5±10.5	−42.0±9.8	−44.4±9.6	−42.1±13.4	0.007**
SS	34.6±7.3	32.4±8.4	31.9±7.3	28.6±7.4	0.019**
PT	7.9±8.5	12.9±8.1	13.7±10.7	18.1±7.8	0.000**
PI	42.6±8.2	45.3±11.1	45.5±12.7	46.7±11.6	0.502
C7-S1 SVA	−7.3±31.0	2.7±28.5	−8.5±24.7	28.4±43.3	0.000**

*P<0.05; **P<0.01.
Abbreviations: C0-1 CA: C0-1 Cobb angle; C1-2 CA: C1-2 Cobb angle; C0-2 CA: C0-2 Cobb angle; C2-7 CA: C2-7 Cobb angle; C2-7 SVA: C2-7 sagittal vertical axis; NT: Neck tilt; TS: T1 slope; TIA: Thoracic inlet angle; TK: Thoracic kyphosis; LL: Lumbar lordosis; SS: Sacral slope; PT: Pelvic tilt; PI: Pelvic incidence; C7-S1 SVA: C7-S1 sagittal vertical axis

0.581 (P = 0.000), and finally, the coefficients between TS and TK were 0.443 (P = 0.011), 0.664 (P = 0.000), 0.529 (P = 0.002), and 0.757 (P = 0.000). The correlations between the above-mentioned cervical parameters and distal spinal parameters showed an increasing trend with age (Figure 2). In addition, the Pearson correlation coefficient between TIA and TK was 0.448 (P = 0.010), 0.486 (P = 0.005), 0.382 (P = 0.031), and 0.479 (P = 0.006), exposing significant differences among groups, but no trend was noted. The correlations between cervical and distal spinal parameters in the four groups are displayed in Table 3.

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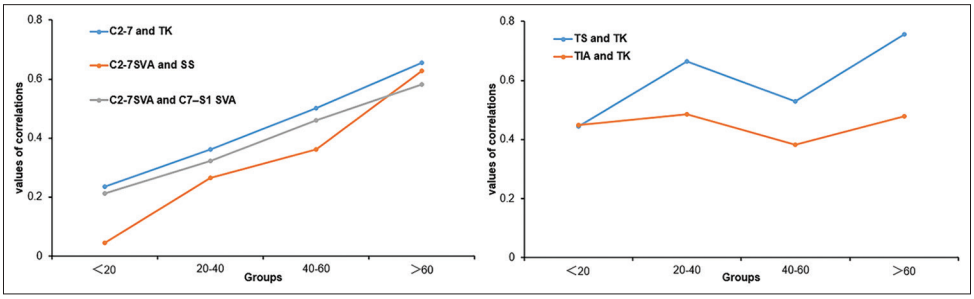

Figure 2. The correlations between the cervical and distal spinal parameters showed an increasing trend with aging, and TIA and TS were significantly correlated with TK, but no definite trend in correlation was detected between TIA and TK.
Abbreviations: TS: T1 slope; TIA: Thoracic inlet angle; TK: Thoracic kyphosis.

4. Discussion

In recent years, an increasing number of studies has reported the correlations between cervical and thoracolumbar pelvic alignments. For instance, Lee *et al.* discovered factors impacting cervical spine sagittal balance in asymptomatic adults and identified the T1 slope as a key factor [8]. At the same time, other scholars have found that C7 SVA is strongly correlated with C2-7 CA [5]; the C7 slope is a link between the occipitocervical and thoracolumbar spine [9]. These results all established the correlations between the cervical alignments and the distal spinal alignments. Our previous studies evinced that some cervical spine parameters tend to vary with aging [7]. Meanwhile, the interaction between cervical and distal spine alignments has also been reported [10,11]. Therefore, the trends of their correlations with aging, which have not been focused on so far, deserve further investigation.

Asymptomatic populations were stratified according to age, and sagittal parameters of the global spine were measured. Our study determined a gradual increase in C1-2 CA, C0-2 CA, C2-7 CA, C2-7 SVA, NT, TS, TIA, TK, PT, and C7-S1 SVA with aging. On the contrary, a gradual decrease in LL and SS was noted with aging. These results are consistent with those of Yukawa *et al.* [12]. Moreover, the results of cervical spine parameters were also comparable to those of our previous research [7], corroborating that sagittal spine parameters show a tendency to change with age. Notably, the loss of lumbar lordosis attributed to disk degeneration has been universally recognized as the initiator of the degenerative cascade, eventually leading to reciprocal changes in other regions [13]. Thoracic alignments serve as a bridge between cervical and distal spinal alignments. As individuals age, the thoracic vertebras begin to manifest adaptive changes, with a wedge-shaped which is narrow at the front and wide at the back [14,15], resulting in physiological kyphosis. Besides, earlier studies described that thoracic kyphosis was progressively aggravated during the aging process owing to the accumulation of mechanical load [14,16], especially in women and elderly osteoporotic patients [17,18]. It is worthwhile emphasizing that thoracic kyphosis steadily worsens over time, and lumbar lordosis concurrently decreases, leading to adaptive adjustments in the spine, such as increased cervical lordosis and decreased pelvic inclination. The synergistic effect of thoracic and lumbar alignments partially explains the trend observed with aging between cervical and distal spinal alignments.

Furthermore, the correlations between cervical and distal spinal parameters were compared among the different groups, and the results demonstrated that the correlations between upper cervical spine parameters (C0-1 CA, C1-2 CA, and C0-2 CA) and distal spinal parameters were all below 0.3, while the correlations between subaxial cervical parameters (C2-7 CA and C2-7 SVA) and distal spinal parameters showed an increasing trend with time. To maintain the sagittal balance of the global spine, changes in the thoracic and lumbar alignment require compensation through the involvement of the cervical spine [19]. Nonetheless, this balance maintenance is supposed to be sufficient through subaxial cervical alignment compensation and does not necessitate the involvement of upper cervical alignments. Therefore, there was a weak correlation between upper cervical spinal and distal spinal parameters.

At the same time, the correlations between C2-7 CA and TK, C2-7 SVA and SS, as well as C2-7 SVA and C7-S1 SVA showed an increasing trend with age in our study. This signified that in the elderly population, there is a strong correlation between cervical lordosis and thoracic kyphosis and between the forward translation of the cervical spine and the forward translation of the global spine. These phenomena occur naturally over time, which might be related to spinal degeneration and atrophy of the paravertebral extensor. Indeed, recent studies corroborated that muscle atrophy and spinal degeneration lead to corresponding alterations in spinal and pelvic alignments [20-25]. Yang [20] found a negative correlation between the atrophy of the paravertebral extensor and cervical sagittal parameters, while Okada [21] reported that changes in cervical spinal alignment contribute to the progression of disc degeneration at C7-T1. In other words, degeneration increased the correlation between cervical lordosis and thoracic kyphosis and that between cervical forward translation and global spine forward translation. We speculate that in the youth population, well-developed cervical paravertebral extensors, intervertebral discs, and intervertebral joints aid in supporting the head, thereby maintaining the horizontal gaze and keeping the head's central gravity line close to the pelvis. However, following paravertebral extensor atrophy, and intervertebral disc and intervertebral joint degeneration, the cervical spine not only becomes more lordotic to compensate for the increased thoracic kyphosis but also leans

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Table 3. Correlations between cervical and distal spinal parameters in the four groups

Cervical parameters	Distal spinal parameters	Group A: ≤20 years	Group B: 21 – 40 years	Group C: 41 – 60 years	Group D: ≥61 years
C0–1 CA	TK	−0.036	0.135	0.191	0.263
	LL	0.108	−0.083	−0.058	−0.168
	SS	0.146	0.114	0.056	−0.151
	PT	−0.139	0.055	0.297	0.113
	PI	−0.016	0.127	0.283	−0.020
	C7–S1 SVA	0.031	0.019	−0.051	−0.190
C1–2 CA	TK	0.238	−0.127	−0.216	−0.119
	LL	−0.086	-0.002	0.151	0.343
	SS	−0.092	0.019	0.026	0.018
	PT	−0.083	−0.028	−0.134	−0.095
	PI	−0.169	−0.006	−0.098	−0.052
	C7–S1 SVA	−0.129	0.085	−0.121	−0.087
CO-2 CA	TK	0.084	0.018	−0.064	0.177
	LL	0.065	−0.109	0.101	0.103
	SS	0.075	0.169	0.066	-0.142
	PT	−0.147	0.037	0.093	0.041
	PI	−0.087	0.156	0.117	−0.063
	C7–S1 SVA	−0.155	0.127	−0.153	−0.268
C2–7 CA	TK	−0.236	−0.362*	−0.502**	−0.655**
	LL	0.105	0.195	0.389*	0.202
	SS	0.136	−0.075	0.221	−0.103
	PT	−0.155	−0.057	−0.177	0.155
	PI	−0.041	−0.099	−0.022	0.039
	C7–S1 SVA	0.022	0.048	0.201	0.163
C2–7 SVA	TK	0.076	−0.141	-0.361*	0.105
	LL	0.116	−0.064	0.134	0.080
	SS	0.045	0.265	0.362*	0.628**
	PT	0.240	−0.378*	0.045	−0.191
	PI	0.291	−0.075	0.247	0.273
	C7–S1 SVA	0.213	0.322	0.460**	0.581**
NT	TK	0.312	0.087	0.068	−0.094
	LL	0.324	−0.064	0.065	−0.273
	SS	−0.299	−0.333	−0.098	−0.185
	PT	0.292	0.255	0.146	−0.134
	PI	0.038	−0.067	0.067	−0.209
	C7–S1 SVA	−0.328	−0.193	−0.161	0.021
TS	TK	0.443*	0.664**	0.529**	0.757**
	LL	0.131	−0.284	−0.213	−0.155
	SS	−0.024	0.243	−0.198	0.331
	PT	0.319	−0.153	−0.068	−0.151
	PI	0.312	0.073	−0.171	0.110
	C7–S1 SVA	−0.003	−0.047	−0.285	0.180
TIA	TK	0.448*	0.486**	0.382*	0.479**
	LL	0.296	−0.235	−0.056	−0.360*
	SS	−0.223	−0.193	−0.220	0.081
	PT	0.370*	0.168	0.115	−0.233
	PI	0.187	−0.024	−0.030	−0.106
	C7–S1 SVA	−0.233	−0.225	−0.338	0.153

*P<0.05; **P<0.01.

Abbreviations: C0-1 CA: C0-1 Cobb angle; C1-2 CA: C1-2 Cobb angle; C0-2 CA: C0-2 Cobb angle; C2-7 CA: C2-7 Cobb angle; C2-7 SVA: C2-7 sagittal vertical axis; NT: Neck tilt; TS: T1 slope; TIA: Thoracic inlet angle; TK: Thoracic kyphosis; LL: Lumbar lordosis; SS: Sacral slope; PT: Pelvic tilt; PI: Pelvic incidence; C7-S1 SVA: C7-S1 sagittal vertical axis

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forward to support the head, thereby increasing C2-7 CA and C2-7 SVA, meanwhile, the more kyphotic the thoracic spine, the lower the degree of lordosis in the lumbar spine. Moreover, the retroverted pelvis, which manifests over time, pushes the trunk forward and thus elevates the C7-S1 SVA. This mechanism may explain the upward trend of correlations between cervical and distal spinal alignment with aging.

In addition, the correlations between TIA and TK in the four groups were significant, but no trends were observed with aging. This result revealed that the correlation between TIA and TK was consistent and not influenced by aging. Correspondingly, the correlation between TS and TK showed an increasing trend with aging, which implied that the impact of TK on TS was more pronounced than TIA during the aging process.

Finally, there were some limitations in this study that needs to be taken into consideration. To begin, the sample size of this study was relatively small, and more subjects need to be enrolled in future studies to reach credible conclusions. Second, the patients were enrolled from South China, and hence, our findings may not be generalizable to the global population. Therefore, future studies should enroll participants from different regions and ethnicities.

5. Conclusion

The alignments of the subaxial cervical spine are closely correlated with distal spinal sagittal alignment during the aging process in the asymptomatic population. In addition, an increasing trend with aging was observed in the correlations between C2-7 CA and TK, C2-7 SVA and SS, and C2-7 SVA and C7-S1 SVA.

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Conflicts of Interest

The authors declare no conflicts of interest in this research.

Ethics Approval and Consent to Participate

This study was approved by Institutional Review Board of The First Affiliated Hospital of Nanchang University, and informed consent was obtained from the patients by the authors.

Consent for Publication

Consent was given by the patients to publish their data and images in this paper.

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REVIEW ARTICLE

Heart failure research paradigms using bedside observation on endothelial muscle common denominators to highlight important translational questions

Pupalan Iyngkaran[1,2*], Fahad Hanna[2], Maximilian De Courten[3], Sharmalar Rajendran[4]

[1]Melbourne Clinical School, The University of Notre Dame, Melbourne, Victoria, Australia, [2]Program of Public Health, Torrens University Australia, Melbourne, Victoria, Australia, [3]Mitchell Institute, Victoria University, Melbourne, Victoria, Australia, [4]Northern Adelaide Local Health Network, South Australia, Australia

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**Corresponding author:*
Pupalan Iyngkaran
Melbourne Clinical School, The University of Notre Dame, Melbourne, Victoria, Australia.
Program of Public Health, Torrens University, Melbourne, Victoria Australia.
E-mail: pupalan.iyngkaran@student.torrens.edu.au

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ABSTRACT

Background and Aim: Congestive heart failure (CHF) imposes a relevant burden on healthcare systems, as it is associated with high morbidity and mortality rates and considerable costs. Within the last three to four decades, there have been revolutionary advancements, particularly in the pharmaceutical industry. In addition, health services research at the population level has also delivered. A third avenue for advancing the clinical management of CHF is to explore established therapies with a new approach. In this perspective, we explore these established concepts and provide impetus for using bedside observations to find improvements in CHF outcomes.

Conclusion: There are potentially new concepts that can be brought to established solutions for CHF. Encouraging observations when delivering established guideline-directed medical therapies are issues that the evidence-based medicine community should factor alongside novel discoveries to improve CHF prognosis. An emphasis on innovating on the known can be considered as an important paradigm for discovery.

Relevance for Patients: Patients with CHF receiving current available treatments have improved outcomes; however, those not improving could be considered under evolving research paradigms.

1. Introduction

Congestive heart failure (CHF) as a syndrome has advanced considerably with the understanding of pathophysiology and in delivering prognostic treatments. The latest guidelines published by American and European cardiac societies provide a comprehensive outline of strategies and proven therapies for holistic CHF disease management [1,2]. Guideline-directed medical therapies (GDMTs) will improve outcomes, nonetheless, the debate will continue in regions where there are poorer outcomes. Thus, there is merit in reflecting on what has been achieved. In particular, understanding where and why there are gaps in achieving trial findings when GDMTs are prescribed at the population level [3-6]. Clinical translation and health services research has addressed some of these external validity factors [7,8]. A second factor on validity that may be intrinsic to patients is not easily standardised for in trials and randomisation and can be masked when data is pooled; importantly, it can be assessed at the bedside when treatments are administered, and responses are observed [9]. There is thus the intersection with post-trial prescribing in the clinical domain, and to fully capture what transpires requires a collaborative mindset and an administrative framework to deliver to patients the GDMT and learn of emerging gaps.

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There are examples of extending innovation from established therapies, from clinical intuition and exceptional bench to bedside translational research. Two such advances in the last decade are the angiotensin receptor-neprilysin inhibitors (ARNIs) as an extension of the renin-angiotensin system and sodium-glucose cotransporter-2 (SGLT-2) inhibitors and extension of incidental observations in diabetes studies [1,2]. These examples highlight the importance of post-trial observations.

Noting it can be decades between such important discoveries, clinicians will undoubtedly question who, how, and when will newer discoveries come along. Feasible contributions clinicians can make in their daily routines are interrogative bedside observations and where relevant, direct a bench connection. For this discussion, we acknowledge that the understanding of cardiovascular disease through vascular endothelium, smooth, and skeletal muscle pharmacology reminisces great achievements in medicine and is an opportunity to ignite debate on gaps and challenges. In this short communication, we first highlight a basic understanding of key CHF processes in the endothelium and skeletal muscle; in the second part, we explore key challenges in epidemiology and drug discovery; and finally, we discuss ideas that may not be traditional; however, the direction of which could be important to find research questions to expand on established therapies.

Heart failure (HF) in this review is focused on HF with reduced ejection fraction (HFrEF). Other forms of HF have different pathophysiology and are not discussed.

2. Gaps Beyond the External Validity of Delivering Guideline-directed Therapies

There are four pillars of CHF pharmacotherapies published in established guidelines (Figure 1) [1,2]. These therapies that were developed over decades are examples of successful clinically translated bench-to-bedside discoveries. CHF affects all organs and utilises many counter regulatory pathways. Some pathways play a greater role in CHF pathophysiology. Other pathways are also important and holistically contribute to chronic disease propagation. Thus, comprehensive care requires a multimodality approach including allied health participation. All established guidelines detail a framework for comprehensive care. Therapeutic response creates a new equilibrium as these pathways navigate from the disease state to the new milieu and vice versa. As there are differences in individual outcomes, if we assume GDMTs have been delivered, according to protocol, this leaves us with several questions: Do differences in response warrant a search for new therapies such as a fifth or sixth pillar; or alternatively exploring the question through renewed bedside observations may highlight pathophysiological clues on how some patients are responding? This post-trial introspective approach allows clinicians to go beyond the grouped outcome data of a trial and individualise an outcome for the patient. Thus, it can then generate new hypotheses to take back to the bench.

There are some examples of this. The A-HEFT study had important implications for treating Black patients with HFrEF [10]. The pioneering hydralazine (arterial dilator)-nitrate (venodilator) Vasodilator HF Trial (V-HeFT trial) in 1986 demonstrated improved survival in HFrEF. In 2004, the African-American HF Trial (A-HeFT trial) improved on mortality reduction of V-HEFT from 34% to 43%. The pathophysiology targeted was primarily reducing intracardiac filling pressures and altering cardiovascular negative remodeling, and secondarily increased nitric oxide (NO) availability both as a donor and with antioxidant properties [11]. In between these studies in 1997, the angiotensin-converting enzyme inhibitor (ACE-i) trials established this as the first pillar in therapy. Here, enalapril superseded the vasodilator combination in mortality. However, among the 215 black versus the 574 white patients, there was no difference in either arm. A speculation was the efficacy of ACE-I in reducing blood pressure in Black patients [12]. In the real world, observations from two studies first showed that in Black patients above 65 years, 18% had an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 and the actual use of proven vasodilators in those who have contraindications to a CHF pillar or who qualify outright was low [10,13-15].

To advance these arguments, we draw on a simple perspective of biological systems, as they are seen as being composed of compartments. External compartments are outside the system. Internal compartments are separated by function, synergy, distance, or other barriers. Importantly, pathways beyond routine facilitation are activated to overcome barriers. Through mediators that act outside a cell or downstream through a cellular receptor counter regulatory mechanism creates the milieu and equilibrium. Several important pathways and downstream links in CHF that *have not* seen revolutionary prognostic treatments, despite playing key roles in its pathophysiology are the endothelium (excluding vasodilator studies) and skeletal muscle.

2.1. Endothelium in HF

In CHF patients, endothelium-dependent vasodilatation is blunted due to abnormal NO production and actions [16-18]. Many CHF treatments aim to restore this balance. Endothelium, the largest organ in the body, originates from embryonic mesoderm. It is a single layer of cells that lines the entire circulatory system, including the heart, blood vessels and lymphatics, and the smallest capillaries of all other organs in the body. Physiologically, vasodilator and constrictor factors, predominately NO and endothelin, regulate structure, function, and dynamism [18]. The endothelium exerts multiple biological effects through endocrine and paracrine signaling pathways. It also responds to various stimuli and has broader actions such as platelet aggregation, leukocyte activation, smooth muscle cell proliferation, neurotransmission, cardiac contractility, anti-tumor, and pathogen, and inflammatory effects, thus maintaining vascular general homeostatic control (Figure 2) [19]. Endothelial dysfunction occurs from an imbalance in vasoregulatory actions, leading to a reduction in flow-mediated dilatation or vasoconstriction in response to agonists, such as acetylcholine. Impaired synthesis and inactivation of the relevant bioactive compounds are then critical to disease development [20].

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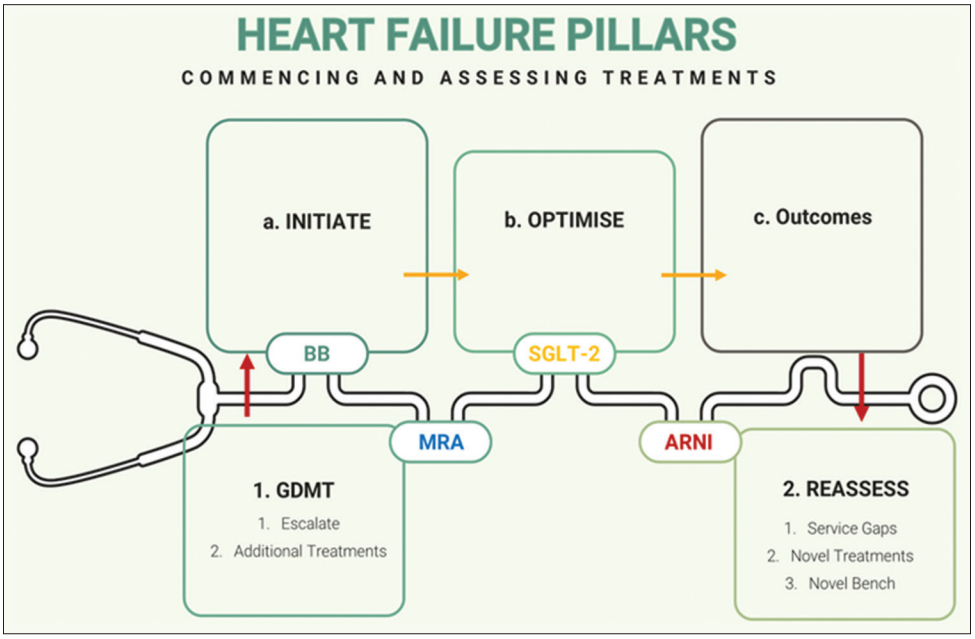

Figure 1. The four pillars of HF therapeutics. The bottom left boxes outline the GDMT: the first pillar ACE-I, now superseded by ARNI, BB, MRA, and SGLT-2 are routine first-line therapies. The top 3 boxes highlight the aim of GDMT treatment from initiation to optimisation and monitoring outcomes. The bottom right box is reassessment if outcomes are not achieved. Importantly, some patients have contraindications or comorbidities. It is vital that individual patient observations and guideline checklist be responsive to detecting gaps in outcomes. It may also be a source for the future discovery. Abbreviations: ARNI: Angiotensin receptor neprilysin inhibitors; BB: Beta-blockers; GDMT: Guideline-directed medical therapy; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose cotransporter-2 inhibitor.

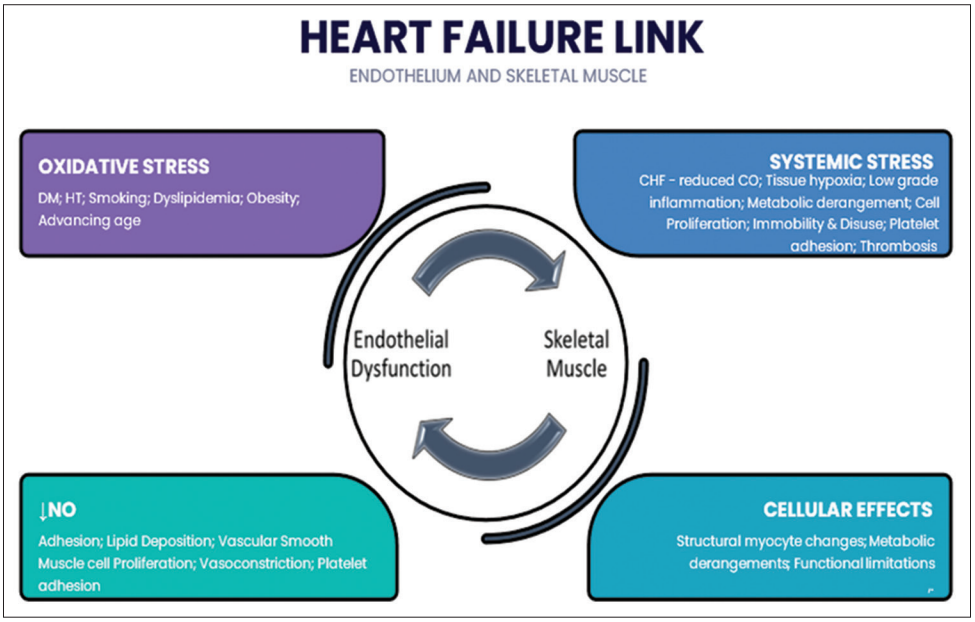

Figure 2. Endothelial skeletal muscle and heart failure (HF) links. Nitric oxide (NO) imbalance and skeletal muscle hypoperfusion and dysfunction are considerations for therapeutics that could be future HF pillars. In common, they are greatly impacted in all stages of the disease. Specifically, traditional risk factors, oxidative stress, NO deficiency, endothelial dysfunction, and skeletal muscle injury are linked in a loop that is both effectors and causes of HF propagation. Endothelial and skeletal muscle responses may potentially have significant impacts on the trajectory that determines recovery and health. The key factors in these pathways that could alter prognosis remain unknown. Bedside observation could play a critical role in identifying those who lag despite optimal care (Adapted from reference 21).

The counter regulatory pathway is NO-cyclic guanosine monophosphate (NO-cGMP). L-arginine is catalyzed by the enzyme NO synthase (NOS) to NO and L-citrulline. There are three isoforms of NOS and its production, functions, and

regulations are well described [14]. The NO-cGMP pathway requires a host of factors including a substrate (L-arginine) and cosubstrates (oxygen and NADPH), enzyme cofactors [Flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and (6R-)5,6,7,8-tetrahydro-l-biopterin (BH4)], intermediary proteins (e.g., calmodulin [intermediary calcium-binding messenger protein]), and trace minerals (e.g., zinc). In CHF, the NO pathway is under stress and a redox state emerges. Elevated production of superoxide radicals and other oxidant species (ROS) with a decline in elimination is defined as oxidative stress. The mitochondria are the main source of ROS that inflicts cellular and DNA damage and reduced NO effects [16,21-24]. With HF, endothelial dysfunction and accumulation of ROS diminish the ability of mitochondria to perform their functions. Oxidative stress is also a common denominator between HF, endothelial dysfunction, and skeletal muscle dysfunction [25-27]. We discuss this in the next section.

2.2. Skeletal muscle and HF

HF induces skeletal muscle myopathy with inflammation, oxidative atrophy, declining strength, acute injury, and impaired regeneration. This myopathy is unique to HF and creates a loop that further declines exercise tolerance [28-31]. These factors are summarised in Figure 2. Essentially, the skeletal muscle is at the forefront of a cycle where its integrity and function are altered by reduced perfusion. In return, the reduced function impairs actions that help the movement of blood in the venous system such as those supported by muscle contraction, and one-way valves. With structural changes, cellular atrophy can lead to apoptosis or permanent dysfunction. There are critical pathways here that trigger these processes. Thus, the NO pathway and skeletal muscles have important links. Impaired blood flow also alters skeletal muscle fatiguability. Endothelial dysfunction and its contributor oxidative stress are directly associated with mitochondrial dysfunction, microvascular dysfunction, exercise intolerance, and insulin resistance in HF [32,33].

There are many contributors to exercise intolerance in CHF, and the direct symptomatic or perceived fatigue attributed to skeletal muscle fatiguability is not clear, although it likely plays a major role. Studies have shown that systolic dysfunction in isolation does not contribute to exercise intolerance or fatigue. A cascade of events with high sympathetic output and low cardiac output leads to reduced perfusion, changes in skeletal muscle metabolism and atrophy, pro-inflammatory cytokines, reduced NO availability, altered oxidation, and glycolysis [28]. Importantly, with the advent of rehabilitation, both NO and muscle changes can be addressed with the right program.

3. Perspective on Observations and Traditional Clinical Laboratory Links

Filling in the clinicopathophysiology gaps was instrumental in the development of the main CHF therapies. Guidelines weaved these therapeutic pillars with ancillary care to shape comprehensive management programs, which work for many patients with improved outcomes and quality of life. Before reflecting on these gains, two points are worth reflecting on; the epidemiology of diseases is transitioning and the risk factors, main etiologies, and demographics, among others, are evolving [5,34]. Today, diastolic HF or HF with preserved ejection fraction (HFpEF) accounts for 50% of all CHF cases and is more prevalent in older adults, particularly females [1]. Second, miscellaneous unanticipated findings can be observed when post-trial real-world data starts emerging, as discussed in the first segment [35]. These are among the strongest arguments to learn and reflect on observations.

3.1. The process of reflecting on achievements

An article published a decade ago by Atkinson highlighted that over the span of 40 years, statins constituted 25% of the top 15 best-selling drugs at the time, and 50% of these drugs entered the market more than 30 years earlier. The author highlighted possible reasons as duration of drug development from synthesis to marketing, and economics which favor copying over innovation. From these observations, Atkinson quoted “Albeit, looking at these figures, a pessimist would be tempted to say that cardiovascular pharmacologists have shown a certain lack of imagination – an optimist would say that there is a large number of potential targets out there just waiting to be discovered and developed” [36]. Whether one or the other perspective is true, here, the pessimistic argument is propagated. For the individual, diseases prosper when the efficiency of communication between any intrinsic feedback loop or extrinsic management option is unhealthy. These communication issues are factors in common for success at the bench (laboratory) and the bedside (health services). With GDMT, the achievement of pharmacotherapy addresses but one component of well-being and is thus prescribed in conjunction with multidisciplinary care and a holistic appraisal of a variety of intrinsic factors. This cannot be better emphasised by the lower attainment of outcomes with proven drugs prescribed at the population level compared to the same drug when used in controlled trials [6]. Thus, an introspection on the epidemiology of the original problem is a vital part of reflecting on achievements.

3.2. Epidemiology: Linking the past to reshaping the future

The last 5 decades have seen stellar advancements in CHF research (Figure 3). The Framingham study, a pioneering population study, was the impetus for an increased understanding of CHF epidemiology[2]. From this point, a revolution in cardiovascular medicine took form. Scientific understanding and technological advancements took many shapes. First, basic sciences led to improvements in diagnostics including cardiac catheterisation which helped improve clinical pathophysiology. This interlink in advancements opened up more areas that delivered pharmaceuticals and extended to device-based technologies. Second, the evidence-based movement (EBM) standardised this process and led to clinical guidelines. Third, from guidelines, post-trial standards were factored in, for example, process of care programs like OPTIMIZE-HF followed by Fonarow *et al.* [8]. We are currently at the point where GDMTs are significant, yet outcomes lag in some areas.

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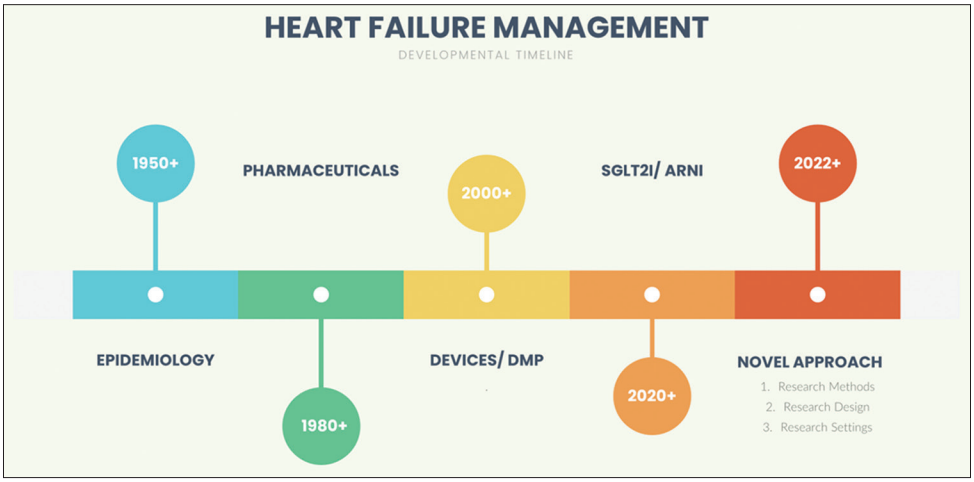

Figure 3. Timelines and potential paradigms for HF with reduced ejection fraction management. The largest gap in research methodology today has been advancing links in hypothesis-generating research and its rapid translation through benchwork. Hypothesis-generating research has its greatest strength in qualitative methodology. Linking these qualitative methods to the bench could prove beneficial to broaden the information from observations to guide the next steps in CHF research. This concept, in a new qualitative (research methodology) paradigm, could be contextualised relative to the direction in the management of chronic diseases from pharmacological, device, physical, to psychological options. Particularly, when the disease trajectory is complex and differs with individual patients. As the permutations are higher, it will thus be hard to get accurate standardisation in CHF patients and research controls. Nonetheless, balancing control, standards, diversity in general population research, or the translational phases could address many outstanding gaps.
Abbreviations: ARNI: Angiotensin receptor neprilysin inhibitor; DMP: Disease management program; SGLT-2: Sodium-glucose co-transporter-2.

In the last several years, the translation of ARNI and SGLT-2 inhibitors as novel pillars of CHF has been important. These guideline-based strategies achieved class 1A indications quickly and unequivocally improved all major cardiovascular outcomes in trials. Nonetheless, like its predecessors, global epidemiology suggests not all patients have seen the full benefits, highlighting ongoing issues in post-translational delivery that require different strategies [35,36]. Despite factoring this, it is interesting to note that however, we look at the epidemiology, the size of the problem is growing, costs are escalating and outcome improvements have not been as significant as other conditions like rheumatic and coronary heart diseases [5,6].

This then poses some questions as to linking clinical observations of the past, the present, and how we identify and shape solutions from them. Two schools of research methodology, qualitative and quantitative, as well as the mixed methods research (MMR) can be applied. There are some important acknowledgements to ponder. First, GDMTs are unequivocally based on quantitative data; second, MMR research is vital for hypothesis generation, however, in the post-trial phase, the logistics of conducting randomised controlled trial (RCTs) to prove these new hypotheses may not be feasible; third, qualitative perspectives on basic sciences, that is, *qualitative molecular epidemiology* is a missing link in this mix. Thus, the question that must be asked is why is it important and how do we link these different research schools to deliver guideline level evidence at the post-trial level?

Class 1A evidence often has a bench and clinical journey to the bedside. The early stages of research are based on the focus of one problem. The journey here is based on the traditional methodology of identifying a clinical problem, identifying a pathophysiological mechanism, and narrowing down the key factors. The result is a key biomarker or therapy that has a significant influence on the disease trajectory. However, as we are realising at a population level as one layer of a problem is unwrapped, others begin to appear. In CHF, with success in improving the acute trajectory of the illness, chronic latent states evolve and interspersed with the slow decline, are acute decompensation and costly readmissions. Let us explore a hypothetical question, to build Class 1A evidence to prevent readmissions. At the population level from current GDMT, we need to consider that there is no absolute cure for CHF. Let's take two examples that offer continuous ambulatory solutions to prevent readmissions, a clinical and invasive example. Both options can act as early identification of decompensation (biomarker) and inform early escalation of acute therapy (e.g., inotropy or diuresis). There have already been studies in this area, predominately with negative results.

i. Chronic disease self-management (CDSM) with a health service-supported model of care such as nurse lead home-based care. The addition of allied health support does improve major adverse cardiovascular outcomes; however, it is resource-intensive and has not translated globally into models of care largely from logistics. CDSM is a viable solution and gold standard trial evidence is still a while away [2,7].
ii. Device-based left ventricular filling pressure assessments are the closest predictors to decompensation. The evidence has been clouded and they are also measuring events later in the decompensation phase [2,38].

Several important lessons could be learned when translating controlled studies: A translation issue is difficult when individualising solutions, as there are many more factors to consider, and we still have lessons to learn on how to deliver evidence

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with wide benefits. This suggests that translational solutions that encompass all comers are difficult and new approaches may be needed. Beyond current GDMT, a holistic and invasive (above) approach has failed to improve outcomes, in patients receiving optimal GDMT. Thus, a holistic trial approach, at some point needs to consider individual factors such as disease chronology and severity itself, demography (age, sex, and ethnicity), and a host of unconventional factors [37]. As there are physiological differences to factor in, this could be important [38-41].

4. Defining the Translational Issue of Complex Care

In considering the issues of translating findings from RCTs and finding solutions for complex and chronic care, this can only be answered when the perspective of the question or problem is encountered and defined. Cause and effect are proven in trials; however, unforeseen gaps are identified in clinical translation. Should these gaps relate to a new disease pathophysiology, new pillars of treatment can be explored as highlighted with NO and skeletal muscle. However, it is gradually being recognised that complex care may determine responses beyond the pathophysiological pathways controlled for in trial settings. This idea could shape post-trial CHF management, and this is discussed.

4.1. Anecdotal evidence for observational paradigms in complex care

Under-representation of demography, ethnicity, gender, and complexity of cases are recognised flaws for translational goals from RCT findings [35,36]. While they are gold-standard for proving causation, the actual issue is not the result but its application when administered to untested heterogeneity, which is the norm in a real-world clinical setting. Registries and anecdotal *post hoc* data are traditional sources for identifying these issues [7]. As an example, among indigenous peoples with chronic diseases in North America and Australasia, this group represented 5.6% of the total population in 172 of 1000 studies reviewed[42]. In cardiovascular trials, from 2015 to 2019, African Americans younger than 65 years only represented 3% of clinical trial participants [39,42]. Among indigenous Australians, established genetic variation with rheumatic heart disease was identified at a locus related to immunity responses (HLA_DQA1-DQB1) [4] and with kidney diseases an uncharacteristically high susceptibility to renal stress, renal failure associated with lower nephron numbers with ACE D alleles [39]. Across the board, there is established evidence of differences in risk factors and diseases in groups of peoples (e.g., race and gender), from single nucleotide polymorphisms to multiple genetic abnormalities, to systems such as cytochomone P450 and receptors such as the adrenergic systems [39].

Specific examples of these paradigms have even come from trials and follow-through with observations in the cohort subgroups and registry of real-world recipients of the medication. The most notable subgroup (African Americans) included in A-HEFT [43] and the ALLHAT [36] study, shaped an important understanding of the pathophysiology of hypertension in this population. Hypertension was observed to be more severe and resistant, from genetic predisposition to retaining salt and water, manifesting biochemically as low renin and aldosterone and overactivity of ENaC [44,45]. Thus, in isolated CHF, as population heterogeneity increases with chronicity and greater complexity, more factors are encountered outside the trial inclusion and this requires ongoing observations to filter potentially significant findings.

4.2. Chronic illnesses and evidence-based medicine

Complex and multimorbid illnesses are confounders to finding proof of causation. Population heterogeneity that contributes to this complexity includes a higher prevalence of traditional and nontraditional risk factors, gender, age, ethnicity, sociodemographics, and multiple chronic comorbid illnesses. These comorbid conditions and demographics can influence the baseline when comparing a treatment and placebo. When we add in the cost of RCTs and the feasibility of bench-to-bedside translation in cost and time, the ability to find meaningful answers for today's chronic ailments such as CHF becomes more challenging, especially post-trial findings. The existing tools are there to allow hypothesis generation, broad observations and means to inform cost-effectiveness when evidence is established. What is different, however, is the level at which we are able to advance these topics and methodologies we utilise.

Thus, the question is how do we better employ the technology that understands pathophysiological mechanisms, for predicting decompensation, preventing readmissions, and reducing costs? What are the population level gaps for CHF? Patients who are good self-managers are invariably better at relaying information to their teams. Good self-management requires a degree of cognitive behavioral changes. However, there are confounders, treatments will improve symptoms, and comorbidities such as renal impairment, coronary artery disease, diabetes, and atrial fibrillation can aggravate HF [7,9]. Symptoms can also be confounded by these conditions and biomarkers like N-Terminal Brain Natriuretic Peptides (NT pro-BNP) can be elevated. The chronology of chronic HF can cause symptoms and biomarker levels to change at varying stages [7,9]. Thus, chronic illnesses have individual fingerprints, while acute illnesses can respond to management strategies along a more singular, universal, and GDMT line. This argument is probably the most relevant, as the health system devises models to address chronic disease cost, outcome, or cost-effectiveness. As there is no fixed baseline of health for patients at first presentation, nor are there predictable trajectories, are individual fingerprints on health needed, and is there a molecular basis for this, and for post-trial scenarios such as predicting early deteriorations?

4.3. Entropy

Could entropy in a medical sense have relevance? If so, it could help start discussions on novel post-trial observational paradigms, which include factoring common denominators in complex cases, or responses in patients with multiple comorbid conditions who demonstrate unexplained treatment responses. A simple definition of entropy is the measure of the amount of energy in a system that cannot contribute to work. Importantly, for our argument,

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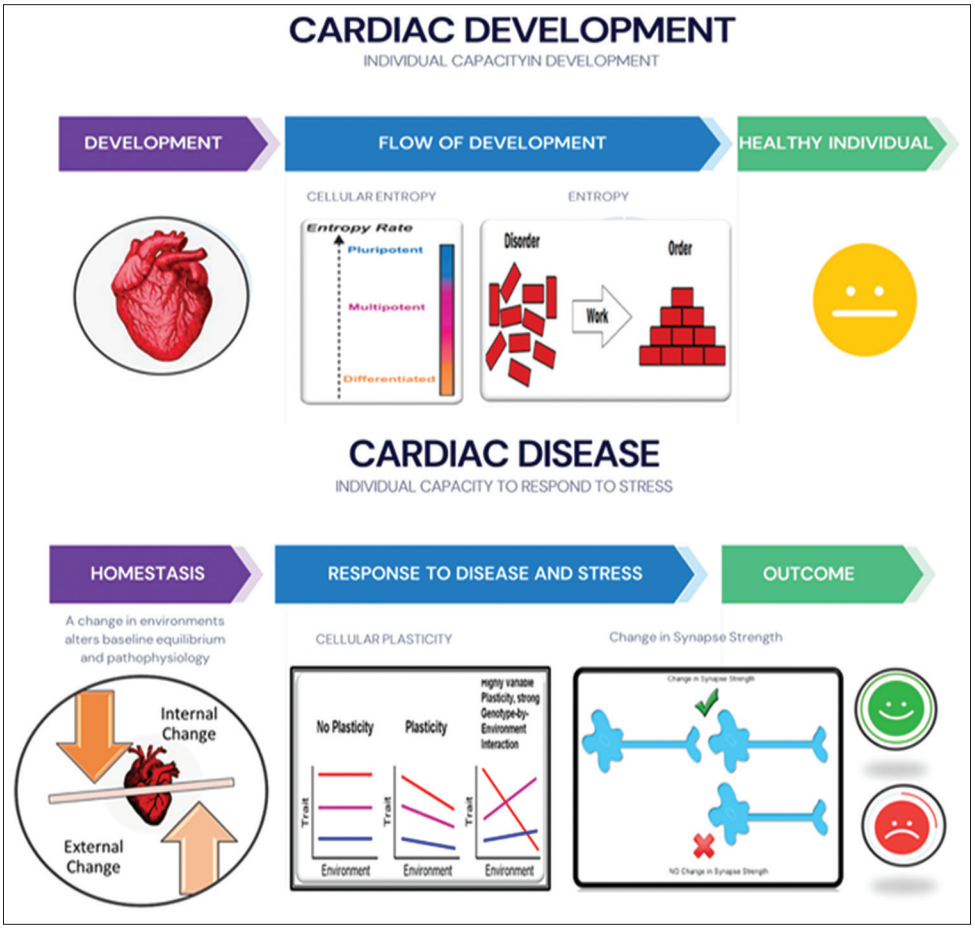

Figure 4. Summary of cellular biology and function. During embryological development cells specialise and commit to certain lineage. Populations of stem cells remain to provide plasticity for new cell regeneration when it is required. Cellular entropy describes the energy that is in the system that allows for the balance of differentiated, multipotent, and pluripotent cells. Entropy describes a systemic process where the cells exchange energy and matter to keep cells functioning normally or alternatively succumbing to external pressures. At present, there are no means to measure this from a clinical perspective. The example below shows an external stimulus that activates internal counter regulatory processes to maintain homeostasis. From the concept of entropy, cellular processes in the counter regulatory pathways have varying degrees of plasticity based on baseline entropy. The result is the ability to change synaptic strength and respond positively to the external stimulus. Wellness and illness could be influenced by entropy. This factor is close to the foundations of a common denominator for systemic health. Further study in this area could reveal useful biomarkers for chronic disease well-being.

it represents a holistic view of a disease state. In cellular development, the human body develops from one cell quickly into an organised symbiotic living organism. The trade-off from this specialisation and organ development is a loss of plasticity. This term is used to define the capability of cells in organisms to adapt to surrounding changes to continue healthy functions. Relevant to entropy are forces that maintain homeostasis. This term is used here to define self-regulation by organisms to adjust to external stimuli to maintain internal stability and function. In fact, the hypotheses we propose around chronic disease revolve around:

i. Understanding the balance between entropy and homeostatic capabilities.
ii. Inactivity and traditional risk alone do not equate to systemic ill health and risk of cardiac decompensation, for example, spinal cord injury patients who are intubated for long periods do not demonstrate worsening cardiovascular function.
iii. From this understanding, we must progressively identify the common denominators that regulate homeostasis, high cellular plasticity/entropy, and resulting low system entropy in patients who are not demonstrating similar benefits despite appropriate treatments. This is a new risk that could be explored further. As a question we can ask, what are we programmed to do at an individual level? How has exposure to factors and comorbidities shaped this response? A summary of these concepts is illustrated in Figure 4.

4.4. Observation to improve guideline-directed care treatment outcomes

What does this concept of entropy have to do with clinical care? What is the nature of the investigations that need to be done? The traditional means to use biochemistry is to identify a change compared to the reference range and associate that with the

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disease. As there can be numerous confounders, this is an example of why this approach is one-dimensional. In CHF, there are aspects of chronic disease care that cannot be mapped by traditional risk scoring. For example, any patient can be at risk of decompensation and resilience is hard to measure. Hence, it does pay to invest in high-value pathophysiological targets and explore their function in multiple dimensions. Entropy appears as a common point that shapes the direction of any individual to stress. The key question is which factor/s can be identified as the rate-limiting one, hence where is the starting point to channel research resources?

Specifically on endothelium and skeletal muscle, endothelial dysfunction alters both cardiac and skeletal muscle function. If the factor is oxidative stress which can be involved in the pathophysiology of HF in the heart as well as in the skeletal muscle; however, the downstream effects at each organ could differ. The treatment effects could also differ. The direction in which patients' well-being moves could vary based on a broader picture. Thus, where entropy is relevant, is that these processes might be predetermined, regardless of conventional risk score predictions. An ability to predict this will allow us to target the patients and deliver the intensive support that may be needed. A better understanding of these mechanisms may enable the development of novel and effective therapeutic strategies against HF, by targeting the factor least likely to respond to GDMT. More specifically, with CHF, there are pleiotropic actions of conventional cardiovascular drugs that could play a greater role.

4.5. Observations and the personalisation of GDMT

An ideal that is yet to take greater shape in medical practice is personalised health parameters, it is hoped that it will achieve optimal individualisation of care. The terminology used varies from personalised [46], customised [47], precision [48,49] care for screening, disease management, and risk prognostication. The tools at hand help phenotypic and genetic profiling and presently computer-assisted analysis of data are also possible. Leopold and Loscalzo [49] that exactness can be counterproductive, thus, as opposed to only identifying the positive, should we identify what does not work, we must invest in identifying causation. GDMT is a checklist, and this can lead to polypharmacy without the intended benefits in some cases, or lack of benefits when treatments are deemed unsuitable. If cost-effectiveness is the standard objective that guides universal systems of care, better use of medicines must be at the heart of this discussion. One place to start is the concept of entropy and identifying early common factors in the failure of therapies. The cost of inefficacious medications is a preventable cost to health systems and patients, in the latter, they can be expressed as disability-adjusted life years. We must thus be mindful of Ehrlich's predication and advance it with thinking on "*It is because we are to exact, we may also fail.*"

5. Conclusions

In this review, we discuss CHF, a chronic and complex cardiovascular syndrome, and explore the paradigm in observing the delivery of GDMT. We have cited examples where post-trial observations have shaped new directions for therapy. As a specific theoretical example, we have contextualised the argument to smooth muscle and endothelium function. An area that is novel in clinical medicine is identifying the sentinel common denominator of the effect to a treatment. This is vital for chronic diseases where there are numerous confounders. While innovation remains critical, we acknowledge that entropy in a clinical sense is theoretical, and our focus is on exploring what is known and reshaping new thinking based on evidence. Bench-to-bedside research today can address common questions and find translatable answers. The margin to maneuver, however, with clinical and basic sciences is decreasing in some areas. Cost-effectiveness remains an important consideration in health services. Specifically, in this paper, we ask the question if we can identify higher risk patients, those who may not achieve the full benefits of GDMT, and are going in the direction that is away from good health? In these cases, investment in conventional guideline care will be costly with little progress. Alternatively, a common denominator can be identified to reverse this. Is there a common denominator here for treatment direction and how do we address this? Improving health and reducing readmissions is a critical consideration as it relates to cost-effectiveness of health policies. *Simple Summary:* Trial evidence extrapolates well to large populations, it may be too complex to broaden applicability further. New concepts that encourage and vet novel observations on clinical outcomes when delivering GDMTs are vital. Entropy is a subjective common denominator to start a dialogue on the more objective pathophysiology determinants in chronic and complex care.

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Conflicts of Interest

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REVIEW ARTICLE

Enhancing clinical and translational research in Africa: a comprehensive exploration of challenges and opportunities for advancement

Gbolahan Olatunji[1], Kokori Emmanuel[1], Osadebamwen W. Osaghae[2], Isarinade Timilehin[1], Nicholas Aderinto[3]*, Muili Opeyemi Abdulbasit[3]

[1]Department of Medicine and Surgery, University of Ilorin, Ilorin, Nigeria, [2]Department of Public Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America, [3]Department of Medicine and Surgery, Ladoke Akintola University of Technology, Ogbomoso, Nigeria

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**Corresponding author:*
Nicholas Aderinto
Department of Medicine and Surgery, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.
E-mail: nicholasoluwaseyi6@gmail.com

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ABSTRACT

Background: Clinical and translational research in Africa faces challenges from limited infrastructure, resource scarcity, and a high disease burden. However, the continent offers promising opportunities with diverse populations, unique genetics, biodiversity, and traditional medicine practices.
Aim: This research aims to comprehensively understand the challenges and opportunities in clinical and translational research in Africa.
Conclusion: We highlight the immense potential for advancing clinical and translational research in Africa while addressing researchers' challenges. By leveraging opportunities, investing in research infrastructure, and prioritizing participant protection, African countries can make significant strides in health-care advancements and contribute to global research efforts. This study presents a roadmap for policymakers, stakeholders, and researchers to collaboratively work toward enhancing clinical and translational research in Africa, ultimately leading to improved health-care outcomes and addressing the continent's unique health needs.
Relevance for Patients: Strengthening clinical and translational research in Africa allows the investigation of disease factors specific to African populations, leading to the development of evidence-based interventions that are more effective in addressing the continent's health challenges. This will ultimately improve health-care outcomes for African patients and impact global scientific knowledge.

1. Introduction

Clinical and translational research stands at the forefront of modern medicine, serving as a crucial catalyst for advancing global healthcare and ultimately improving patient outcomes [1]. It bridges fundamental scientific discoveries and their practical application in clinical settings, enabling the translation of scientific knowledge into tangible benefits for patients [2]. Clinical and translational research results from the bedrock of evidence-based medicine, empowering health-care professionals to make informed decisions and provide high-quality care [3]. Despite significant progress in clinical research worldwide, there remains a striking disparity in the advancement of clinical and translational research within the African continent. Africa is emerging as a significant player based on its size, demographics, economic growth, and commitment to improving healthcare and life expectancy [4]. With a population of over 1.34 billion people, projected to reach two billion by 2038 and 2.5 billion by 2050, Africa constitutes over 17% of the global population [5]. Moreover, it bears the highest disease burden globally, accounting for approximately 25% of all diseases [6]. These factors create an opportune environment for conducting clinical

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trials. However, despite these advantages, Africa's contribution to the total number of clinical trials remains dismally low, accounting for <2% of the global total [7]. This disparity poses a formidable challenge, as it impedes the health-care sector's ability to effectively address the African population's unique and diverse healthcare needs. Moreover, it hinders the development of context-specific solutions that are tailored to the intricacies of African communities, cultures, and environments. Consequently, the gaps in clinical and translational research in Africa impact the region and have broader implications for global health equity and cooperation [8]. The multifaceted nature of this challenge becomes evident when considering the rich diversity of Africa's health-care landscape. The continent is home to many cultures, languages, and health systems, each presenting complexities and intricacies [9]. The burden of infectious, non-communicable, and emerging health threats increases the urgency of strengthening clinical and translational research endeavors [6]. Moreover, Africa's unique genetic diversity necessitates region-specific studies to unravel the genetic basis of diseases and their treatment responses, which can differ significantly from other parts of the world [10].

Investing in clinical and translational research in Africa is essential to uncover invaluable knowledge and cultivate effective healthcare interventions to overcome this disparity. Investing in clinical and translational research in Africa is vital, as it promises to uncover invaluable knowledge and cultivate effective solutions. By conducting rigorous research specific to the African context, researchers can gain insight into the intricacies of these diseases, their impact on diverse populations, and the most effective strategies for prevention, diagnosis, and treatment [10]. Such research is essential for developing evidence-based guidelines and treatment protocols tailored to unique health-care needs. Without comprehensive research, health-care providers may rely on interventions primarily tested in other regions, which may not fully address the complexities and nuances of African healthcare [11].

Nevertheless, several significant obstacles exist for clinical and translational research in Africa. One of the most pressing challenges is the lack of adequate funding, which hampers the scale and scope of research initiatives. In addition, the need for more research infrastructure and limited access to cutting-edge technologies impedes the efficiency and effectiveness of research efforts. The brain drain phenomenon further exacerbates the challenge, leading to losing essential expertise within the continent. Addressing these issues requires collaborative efforts and innovative solutions that harness the strengths of international partnerships while fostering local research capacity and retention strategies.

Beyond the practical challenges, cultural barriers and regulatory dilemmas often impede clinical and translational research in Africa [12]. The diversity of cultural norms and beliefs necessitates a sensitive and nuanced approach to research design and implementation [6]. Similarly, the ethical implications of research involving vulnerable populations must be carefully navigated to protect participants' rights and dignity. This study aims to identify and address the barriers hindering the progress of clinical and translational research in Africa. By analyzing current challenges related to research infrastructure, funding, brain drain, cultural considerations, and regulations, the study will provide valuable insights to guide future efforts. The goal is to propose targeted solutions and strategies that enhance research capacity, foster collaborations, and ensure ethical practices. Ultimately, this study seeks to unlock Africa's full research potential and improve health-care outcomes for the diverse African population.

2. Current State of Clinical and Translational Research in Africa

Clinical and translational research in Africa is progressing significantly and experiencing remarkable growth [13]. However, it is important to note that the research landscape varies between different countries and regions of the continent [14]. Africa faces a unique set of challenges and opportunities in the field of research, including limited resources, inadequate infrastructure, political instability, and a high burden of infectious diseases [15,16]. Despite these obstacles, notable developments and initiatives have strengthened African clinical and translational research efforts [17].

One crucial aspect of these efforts is the ongoing focus on improving research infrastructure and building research capacity in African countries. Collaborations between African institutions, international partners, and organizations such as the African Academy of Sciences and the African Union have been pivotal in driving these initiatives [18]. Through collaborative initiatives, partnerships have been formed between African institutions, global organizations, and international research institutions to promote collaboration and knowledge sharing. Notable examples of such initiatives include the African Network for Drugs and Diagnostics Innovation, the African Collaboration Centre for Pharmacovigilance (AFRO-Pharm), and the African Partnership for Chronic Disease Research [19]. These collaborations have led to significant outcomes, including establishing training programs, research networks, and infrastructure development projects [19]. The primary objective of these initiatives is to enhance the abilities of African researchers and institutions to conduct high-quality research. By providing training opportunities, researchers are equipped with advanced research methodologies, data analysis skills, and a strong understanding of ethical considerations, enabling them to address their respective fields' unique challenges and opportunities effectively.

In addition to infrastructure and capacity building, research networks have emerged as valuable mechanisms for fostering collaboration and knowledge exchange among African researchers [20]. These networks connect scientists from different institutions and disciplines, facilitating sharing ideas, resources, and expertise. Through collaborative research projects and multicenter studies, research networks promote interdisciplinary approaches and enhance the overall quality and impact of research results.

Recognizing the importance of physical and technological resources in conducting high-quality research, infrastructure

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development projects have become a key component in improving research capacity in Africa [21]. These projects focus on establishing or upgrading laboratory facilities, research centers, and clinical trial sites, ensuring researchers have access to modern equipment, well-maintained facilities, and reliable resources. This infrastructure support enables researchers to carry out their work efficiently and effectively.

Collaborations with international partners benefit research capacity building in Africa [22]. These partnerships often provide funding, technical assistance, and mentorship, further strengthening the research capabilities of African institutions [22]. The transfer of knowledge, expertise, and technology from international partners to African researchers contributes to the overall growth and advancement of research in the region. The ultimate goal of these collective efforts is to empower African researchers and institutions to conduct impactful research that addresses the specific health challenges African populations face. By investing in research infrastructure and capacity building, African countries can generate locally relevant evidence, inform health policies, and improve health-care delivery. Consequently, these efforts lead to better health outcomes for African communities.

3. Challenges in Clinical and Translational Research in Africa

Clinical and translational research in Africa faces several significant challenges that must be addressed to foster progress and development in the field Table 1. One primary challenge is the limited availability of research infrastructure and resources. Despite remarkable contributions from some African-led research centers, many African universities and institutions still need more cutting-edge laboratories, advanced technology, and well-equipped facilities for conducting rigorous clinical trials and translational research [23]. This dearth significantly hampers the scope and quality of research conducted on the continent, impeding scientific advancements and hindering the realization of Africa's full research potential. In contrast, research institutions in developed nations often boast state-of-the-art laboratories with cutting-edge technology and facilities that enable groundbreaking research [24]. This disparity needs to be improved for African researchers, limiting their ability to compete globally and collaborate effectively with international counterparts.

Nevertheless, some shining examples of African-led research centers have made substantial contributions to the scientific community. One such example is the South African Tuberculosis Vaccine Initiative (SATVI), a world-renowned research center dedicated to developing new vaccines for tuberculosis [25]. SATVI's pioneering work showcases the potential for African-led research to drive innovation and address critical healthcare challenges that disproportionately affect the continent. Similarly, the African Institute for Mathematical Sciences (AIMS) stands as a pan-African network of centers of excellence that provide advanced education in mathematical sciences to students from across the continent [26]. By nurturing talent and fostering interdisciplinary collaborations, AIMS exemplifies the transformative impact of African-led initiatives in promoting research and knowledge dissemination within and beyond the region. Despite these notable success stories, the need for cutting-edge research facilities and advanced technology is a significant barrier to fully unlocking Africa's research potential. Addressing this scarcity requires targeted efforts from both local and international stakeholders, including governments, funding agencies, and private institutions. By investing in developing and modernizing research infrastructure, Africa can enable researchers to thrive and contribute meaningfully to global scientific advancements.

More financial support and the need for grants present formidable barriers to clinical and translational research endeavors in Africa. These projects require substantial funding to cover essential aspects such as personnel remuneration, purchasing laboratory supplies, efficient data management, and participant recruitment. Unfortunately, funding availability is often limited, leading to project delays, compromised research outcomes, and difficulties in attracting and retaining highly skilled researchers [27]. Remarkably, Africa receives a mere 1% of the global investment in research and development (R&D), with Egypt, Nigeria, and South Africa contributing up to 67% of the total domestic spending on R&D in the region while holding a meager 0.1% of the world's patents [28]. Such

Table 1. Challenges, opportunities, and policy recommendations in advancing clinical and translational research in Africa

Challenges	Opportunities	Policy recommendations
Limited research infrastructure	Diverse populations and unique genetic backgrounds	Increase research funding and budget allocation
Scarcity of resources	Abundant biodiversity	Establish research partnerships and networks
High burden of diseases	Traditional medicine practices	Promote ethical research practices and oversight
Ethical considerations and regulatory hurdles	Collaboration and knowledge sharing among institutions	Enhance data management and sharing mechanisms
Data collection and management challenges	Public-private partnerships	Foster collaboration between African institutions and international partners
Lack of trained healthcare professionals and researchers	Integration of digital health technologies	Invest in health-care workforce training and capacity building
Access to advanced technologies and equipment	Leveraging international collaborations	Provide access to advanced technologies and equipment
Language and cultural barriers	Strengthening research capacity and training	Address language and cultural barriers
Funding constraints	Investing in research infrastructure	Develop sustainable funding mechanisms and grants
Political and socioeconomic factors	Patient-centric approach to research	Create a supportive policy environment for research

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a stark disparity underscores the significant funding gap that the continent faces.

Furthermore, ethical and regulatory challenges pose significant implications for clinical and translational research in Africa, affecting the conduct of studies involving human subjects [6]. Establishing and maintaining strong ethical guidelines and regulatory frameworks are paramount to safeguarding the rights, welfare, and safety of research participants while upholding the integrity of research data. However, implementing and enforcing these standards vary significantly across African countries, leading to inconsistencies, delays, and ethical dilemmas [29]. Establishing and maintaining strong ethical guidelines and regulatory frameworks are crucial to protect research participants' rights, welfare, and safety of research participants and ensuring the data's integrity. However, implementing and enforcing these standards can vary across African countries, leading to inconsistencies, delays, and ethical dilemmas [29]. One example of such challenges is the variation in ethical review processes [6]. Countries often have different procedures for reviewing research protocols, obtaining informed consent from participants, and ensuring the ethical conduct of studies [6]. This inconsistency can create confusion and hinder the timely initiation of research projects.

One prominent challenge in research ethics governance is the historical context of its development [29]. Research governance structures have often been a reactive response to past unethical research practices [30]. Despite increased research activity in Africa over the past decade, driven by pressing psychosocial and health-related challenges, improvements in the governance and oversight of human research practices have yet to be commensurate with this growth [31]. This has, unfortunately, created a window for exploitative research funded by resource-rich countries, conducting studies in Africa that might be considered unethical in countries with more established and stringent research regulatory frameworks.

In some cases, lengthy review processes can delay the start of studies, affecting the ability to address urgent health concerns or introduce new interventions. The availability and accessibility of research ethics committees (REC) often differ across African countries [32]. Some regions may need more resources and infrastructure to establish and maintain RECs, which can delay the approval of research projects [32]. This situation can hinder the progress of studies and discourage researchers from conducting research in those areas. In addition to the challenges related to ethical review processes, there are disparities in the understanding and applying ethical principles and guidelines among researchers, health-care providers, and participants [32]. Cultural beliefs, language barriers, and limited awareness of research ethics can influence participants' understanding of the risks and benefits of participating in studies [33,34]. This lack of understanding impacts the validity and quality of informed consent, potentially compromising participant autonomy and the reliability of research findings. Similarly, linguistic and cultural barriers also challenge clinical and translational research in Africa [33]. The continent is characterized by linguistic diversity and cultural variations, which inhibit effective communication, participant recruitment, informed consent procedures, and data collection efforts [33]. Cultural beliefs, traditions, and stigmas also influence the willingness of individuals to participate in clinical studies [35].

Brain drain and limited research capacity present significant obstacles to clinical and translational research in Africa. Disturbingly, Africa's contribution to the world's scientific output has dwindled from 0.5% to a mere 0.3%, reflecting the region's struggles in retaining scientific talent [36]. The continent is grappling with a continuous brain drain of scientists, engineers, and technologists, further exacerbating the research capacity gap. Africa accounts for only 3.6% of the world's scientific workforce, indicating a severe shortage of research professionals [36]. The overwhelming concentration of 80% of scientific research in a handful of industrialized countries underscores the stark disparity in research capabilities worldwide [36]. This disparity is particularly acute in sub-Saharan Africa, where the migration of young and educated professionals significantly affects an already scarce pool of human capital [37]. The departure of skilled individuals from the region robs Africa of much-needed expertise, hindering the establishment and growth of research initiatives and institutions. This brain drain phenomenon significantly impairs Africa's capacity to conduct clinical and translational research at the level needed to effectively address the continent's diverse health-care challenges. Losing talent to more developed regions denies Africa the expertise required to innovate, develop context-specific solutions, and drive scientific advancements. The departure of skilled researchers and health-care professionals from the continent seeking improved opportunities and resources has significant consequences. This ongoing exodus results in a loss of valuable expertise, leading to a weakened research capacity that impedes Africa's ability to effectively address its communities' unique health challenges.

The critical deficit of scientists and researchers in Africa is a pressing concern that requires urgent attention. The need for more skilled professionals directly affects the region's ability to conduct impactful research and develop innovative solutions to address the specific health needs of its diverse populations. With a sufficient pool of researchers, the ability to generate locally relevant evidence and implement context-specific interventions is greatly improved. The consequences of this brain drain are far-reaching. The loss of talented individuals deprives African countries of the intellectual capital needed to advance clinical and translational research and hampers the overall progress of the health-care system. The absence of skilled researchers and health-care professionals diminishes the quality of care provided, reduces the capacity for scientific discoveries, and undermines the development of effective health policies and interventions tailored to the local context.

4. Policy Recommendations and Future Directions

Improving the health infrastructure in Africa is crucial to meet the demands of clinical and translational research on the continent. Adequate health infrastructure, including hospitals, clinics, laboratories, and specialized care facilities, is essential to

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conduct high-quality research and provide the necessary resources for researchers and health-care professionals (Figure 1).

Investing in research facilities and laboratories is paramount in advancing clinical and translational research capabilities in Africa. Beyond enabling cutting-edge research, these state-of-the-art facilities are pivotal in attracting and retaining skilled researchers and scientists within the region. By providing researchers with an environment replete with advanced technologies and resources essential for their work, these facilities retain local talent, mitigate the adverse effects of brain drain, and cultivate a vibrant research community that augments scientific progress in Africa. Optimizing the impact of research facilities necessitates emphasizing capacity building and training initiatives [38]. The effective utilization of these resources is ensured by affording researchers, technicians, and support staff access to specialized training in operating advanced laboratory equipment and employing state-of-the-art research techniques. These training programs should encompass technical skills and underscore the significance of research ethics in upholding rigorous scientific integrity and responsible research conduct.

Promoting collaboration and networking among research institutions within Africa and with international partners constitutes a pivotal strategy in enhancing research capabilities across the continent. One prominent initiative facilitating such collaborations is the African Research and Education Network (AfREN), an ambitious project aiming to accelerate the development of African National Research and Education Networks while serving as a catalyst for global research and education cooperation [39]. Spearheaded by the Association of African Universities and generously funded by the European Union, the AfREN project adopts a visionary approach by aligning its objectives with the United Nations sustainable development goals, thus ensuring a holistic and impactful research agenda that addresses pressing societal needs. In tandem with AfREN, other research networks have emerged in Africa, further enriching the research landscape and contributing to the continent's scientific progress. One noteworthy example is the Tertiary Education and Research Network of South Africa (TENET), which has been at the forefront of providing exceptional research and education networking services for over two decades [40]. Through its collaborative inter-networking approach, TENET has facilitated seamless communication and data sharing among universities, science councils, and related research institutions, fostering a climate of cooperation and knowledge exchange that enhances research capabilities and educational opportunities. In addition, the African Research Universities Alliance exemplifies the power of collaboration in forging a common vision among universities from diverse countries and historical backgrounds [41].

These research networks epitomize the continent's commitment to promoting research collaboration and fostering an environment that nurtures academic excellence. By facilitating networking and inter-institutional partnerships, these initiatives create opportunities for researchers and students to engage in joint research projects, participate in cross-disciplinary endeavors, and gain exposure to diverse perspectives and methodologies.

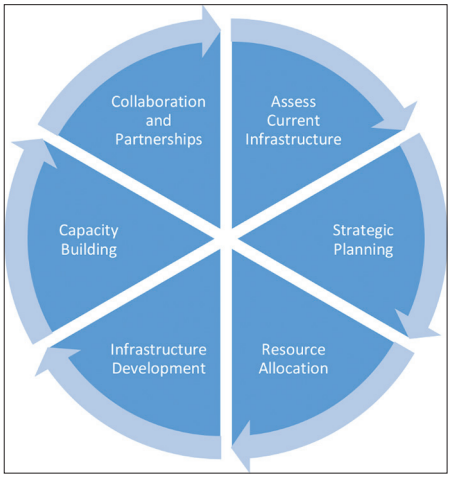

Figure 1. Research infrastructure strengthening process.

Moreover, networking extends beyond Africa's borders, enabling fruitful collaborations with international partners, thus positioning African research globally and enriching the broader scientific discourse. Collaborative partnerships with established research institutions from other regions facilitate knowledge exchange, access to funding opportunities, and the undertaking of joint research endeavors [42]. Such collaborations foster a convergence of global expertise and best practices, elevating the quality and scope of African research.

Nonetheless, several challenges may impede the successful implementation of research facility investments. Foremost among these challenges are funding constraints, as the establishment of state-of-the-art laboratories necessitates substantial financial resources, which may pose difficulties, particularly in resource-limited settings [43]. Policymakers and stakeholders must prioritize research funding and explore innovative funding mechanisms to ensure sustainable support for developing research infrastructure. Moreover, vigilant attention must be accorded to infrastructure maintenance once research facilities are established. Timely maintenance and upgrading equipment and infrastructure are indispensable in avoiding suboptimal research outputs that could hinder scientific progress. Robust maintenance plans and the allocation of resources for ongoing support are, therefore, essential considerations.

Furthermore, the assurance of a proficient workforce competent in operating and leveraging advanced laboratory equipment assumes critical importance. Brain drain and limited research capacity in Africa could precipitate a shortage of qualified professionals, necessitating focused efforts on education, and training initiatives. Capacity-building programs should encompass academic training that equips students and researchers with the necessary skills and knowledge to utilize research facilities and conduct high-quality research effectively. In addition, navigating complex regulatory and administrative processes could present challenges in establishing research facilities and obtaining requisite approvals. Streamlining these processes and fostering a conducive regulatory environment are vital to expedite research progress and create a research-friendly atmosphere.

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In addition to physical infrastructure, integrating digital health technologies is a pivotal enabler for advancing clinical and translational research in Africa. By embracing electronic medical records, telemedicine platforms, and health information systems, the continent can unlock new dimensions of research potential. These transformative technologies play a multifaceted role in enhancing various aspects of the research landscape, ultimately revolutionizing clinical and translational studies' quality, efficiency, and scope [44].

Digital health technologies offer a wealth of benefits to research endeavors in Africa. One primary advantage is their capacity to streamline data collection, management, and analysis processes [45]. Electronic medical records provide a standardized and efficient record-keeping approach, facilitating seamless patient data access across health-care facilities [46]. This enhances the continuity of patient care and enables researchers to access comprehensive and real-time health information for their studies. As a result, data accuracy and completeness are greatly improved, ensuring the validity and reliability of research findings.

Furthermore, telemedicine platforms offer a groundbreaking solution to the geographical barriers often faced in researching vast and diverse African landscapes [47]. Researchers can remotely consult with patients and health-care professionals through telemedicine, enabling a more inclusive and representative participant pool. This virtual connectivity expedites the recruitment process and ensures broader participation, encompassing remote and underserved regions. Consequently, research studies become more representative of the African population, leading to more generalizable and applicable results. The efficient sharing of health data facilitated by digital health technologies fosters unprecedented collaboration among researchers, healthcare institutions, and policymakers. By breaking down silos and promoting data interoperability, these technologies create a collaborative ecosystem where research findings can be shared and disseminated rapidly. This not only accelerates the pace of research but also cultivates a culture of knowledge exchange and scientific cooperation within the African research community.

However, despite the promising potential of digital health technologies, implementing these innovations comes with challenges. The first significant hurdle is the need for robust data privacy and security measures. Safeguarding sensitive patient information is paramount to maintaining trust and compliance with ethical standards [48]. Therefore, policymakers must invest in establishing robust data protection frameworks, ensuring that patient privacy is prioritized throughout the research process. Moreover, technology adoption requires substantial initial investments and ongoing maintenance costs [48]. For many African countries with limited resources, securing adequate funding for these technologies can take time and effort. Policymakers and stakeholders must collaborate to devise sustainable financing models, exploring public-private partnerships and international cooperation to bridge the funding gap. Integrating digital health technologies also demands a skilled and tech-savvy workforce [49]. Training health-care professionals, researchers, and research coordinators in utilizing these technologies effectively are essential to maximize their impact on clinical and translational research. This training should encompass technical skills and emphasize research methodologies, data management, ethics, and adherence to Good Clinical Practice (GCP) guidelines. Ensuring continuous professional development and supporting capacity-building initiatives can nurture a competent research workforce capable of harnessing the full potential of digital health technologies.

Public-private partnerships and collaborations between African institutions, international organizations, and private sector entities hold immense potential for enhancing health infrastructure across the continent. The African Development Bank (AfDB) has taken a proactive step in addressing Africa's health infrastructure deficits by releasing its Strategy for Quality Health Infrastructure in Africa 2021 – 2030 [50]. This strategy is a response to the urgent need to improve national health infrastructure, which has been underscored by the challenges posed by the COVID-19 pandemic and other health crises. The AfDB, drawing on its core expertise in infrastructure development, aims to bridge the existing gaps and provide essential support to regional member countries seeking to strengthen their health-care systems. Such partnerships can bring additional resources, funding, and expertise to support developing and maintaining health-care facilities and research infrastructure [31]. For example, collaborations with pharmaceutical companies or medical equipment manufacturers can provide access to cutting-edge technologies and resources that might otherwise be challenging. However, despite the promising potential of these strategies, several challenges may impede their successful execution. Key barriers include limited financial resources, bureaucratic hurdles, and varying regulatory environments across African countries. To overcome these challenges, stakeholders must align their efforts and work together to overcome barriers. Policymakers and international organizations must be crucial in facilitating dialogue and fostering an enabling collaborative environment.

Moreover, it is essential to prioritize the equitable distribution of health infrastructure across regions and populations within African countries. By ensuring that research facilities and resources are accessible to underserved areas, rural communities, and marginalized populations, clinical and translational research benefits can reach a broader population segment. This inclusivity helps address health disparities and ensures that research findings apply to diverse populations.

Governments in African countries must display an unwavering dedication to research advancement by allocating a substantial portion of their budgets to support clinical and translational research endeavors. Regrettably, public funding for research in many African countries has been inadequate. African countries must grapple with more financial support for research initiatives. In 2006, member countries of the African Union committed to spending 1% of their gross domestic product (GDP) on R&D, a pledge to foster scientific progress and innovation. However, the continent's actual funding for research stood at a mere 0.42% by 2019, starkly contrasting the global average of 1.7% [28]. The disparity in research funding is evident in individual African countries as well. For instance, Kenya allocates approximately

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0.8% of its GDP to research, South Africa dedicates 0.75%, and Egypt invests 0.6% [28]. These figures highlight the considerable variation in financial commitment to research among African nations. To address this issue, governments must prioritize research and acknowledge its critical role in advancing healthcare, technology, and overall socioeconomic development. Meeting the 1% GDP target of the African Union sets is a pivotal step towards fostering a thriving research ecosystem across the continent. Such increased funding will enable the establishment and expansion of research facilities, the recruitment and retention of skilled researchers, and the implementation of cutting-edge research projects.

Moreover, governments should consider adopting long-term national research funding strategies that prioritize research across various sectors, including healthcare, agriculture, technology, and the environment. Consistent and sustained funding is crucial for fostering a culture of scientific inquiry and innovation, leading to tangible benefits for the population. While allocating increased funding is essential, governments should also focus on the transparent and efficient utilization of research resources. Strengthening research governance and implementing rigorous financial management practices will ensure that funds are optimally utilized and directly contribute to meaningful research outcomes. African governments should actively engage with international organizations, development agencies, and private sector partners to attract additional research support. Collaborative funding initiatives can provide much-needed resources for research projects that address critical health challenges and contribute to global scientific knowledge.

However, achieving substantial increases in research funding takes time and effort. Governments may need to work on competing priorities, limited resources, and bureaucratic complexities. Addressing these barriers requires effective advocacy by the research community and establishing partnerships with key stakeholders. Governments must recognize that investing in research yields long-term benefits, including improved health-care outcomes, economic growth, and the development homegrown solutions to regional challenges.

International collaboration and donor support are pivotal in augmenting funding for African research [51,52]. Governments and research institutions should seek partnerships with international organizations, donor agencies, and philanthropic foundations. By cultivating robust relationships with these entities, African countries can access additional resources and secure sustainable funding for research initiatives. Engaging with funders with a vested interest in African health issues is imperative, and capitalizing on their expertise and financial support is imperative.

Advocacy and raising awareness about the importance of research are instrumental in garnering support and funding. African governments, research institutions, and advocacy groups must collaborate to highlight the significant impact of clinical and translational research on health outcomes and development in the region. Educating policymakers, communities, and the general public about the value and potential of research increase the likelihood of securing increased funding and resources. To attract private sector investment, African countries can establish an enabling environment for collaboration between research institutions and industry. This can be achieved by establishing public-private partnerships that incentivize private-sector involvement in R&D. Governments can offer tax incentives, streamline regulatory processes, and provide intellectual property protection to encourage private sector engagement and investment in clinical and translational research.

Strengthening research capacity and infrastructure is crucial for attracting funding. African countries should invest in the training and development of local researchers, thus creating a skilled workforce capable of driving high-quality research. Furthermore, improving the research infrastructure, including state-of-the-art laboratories, well-equipped research centers, and suitable clinical trial sites, is essential for conducting rigorous studies. By demonstrating their commitment to building research capacity, African countries can instill confidence in funders and attract increased financial support.

Promoting and nurturing collaborations among African research institutions is essential to advancing clinical and translational research. By fostering a culture of cooperation and knowledge sharing, African researchers can harness the power of collective expertise and resources to achieve greater scientific advancements. Collaborative research projects provide a platform for pooling diverse perspectives, expertise, and methodologies, leading to a more comprehensive and nuanced understanding of complex health challenges specific to the region [53]. One of the key advantages of collaborations lies in the ability to undertake larger and more impactful studies [53]. By uniting their efforts, African research institutions can tackle ambitious research questions that require extensive data, resources, and multi-site collaborations. Such joint endeavors enhance studies' statistical power, yielding more robust and reliable research outcomes. In addition, collaboration facilitates the exchange of ideas and best practices among researchers. Sharing knowledge and experiences across institutions and disciplines promotes continuous learning and innovation. Through such interactions, researchers can learn from each other's successes and challenges, identify novel research approaches, and adapt successful interventions to different contexts.

Interdisciplinary collaborations, in particular, hold significant promise for clinical and translational research. Researchers can approach complex health issues from multiple angles by bringing together experts from diverse fields such as medicine, public health, social sciences, and engineering. This integrative approach often leads to more comprehensive solutions that address the multifaceted nature of health challenges in Africa. Furthermore, collaborations increase the attractiveness of research projects for funding opportunities. Funding agencies and donors often prioritize projects with a strong collaborative component due to their potential for greater impact and sustainability. By presenting a unified front, African researchers can attract funding from international organizations, philanthropic foundations, and governmental bodies, bolstering their research capacity and accelerating scientific progress.

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Developing robust regulatory bodies is essential to promote and oversee clinical and translational research in Africa. These bodies play a crucial role in ensuring the safety of research participants, upholding ethical standards, and maintaining the integrity of research data. However, establishing and strengthening regulatory bodies in Africa are an ongoing process that requires concerted efforts and collaboration among various stakeholders. One key step in developing regulatory bodies is enacting comprehensive legislation that provides a legal framework for research activities. This legislation should encompass informed consent, participant protection, data privacy, and ethical review processes. Regulatory bodies can effectively regulate research practices and hold researchers accountable for ethical misconduct by having clear and enforceable laws. Another crucial aspect of developing regulatory bodies is the establishment of independent ethics review committees or institutional review boards (IRBs) [54]. These committees are responsible for evaluating the ethical aspects of research protocols, ensuring that the rights and welfare are protected, and providing oversight throughout the research process. To ensure a comprehensive and unbiased evaluation of research proposals, IRBs should comprise diverse experts, including health-care professionals, ethicists, legal experts, and community representatives.

In addition to legislation and IRBs, capacity building is vital for the effective functioning of regulatory bodies. Training programs should be developed to enhance the knowledge and skills of regulatory staff, researchers, and members of ethics review committees [55,56]. These programs can cover various topics, including research ethics, regulatory compliance, data management, and GCP. By investing in capacity building, regulatory bodies can ensure their members have the experience to navigate the complex clinical and translational research landscape. Furthermore, collaboration between African countries is essential to harmonize regulatory standards and facilitate mutual recognition of research approvals [57]. The African Union and other regional organizations can be essential in promoting collaboration and harmonization efforts. By establishing common guidelines, sharing best practices, and creating platforms for knowledge exchange, regulatory bodies can work together to streamline research processes, improve efficiency, and enhance the credibility of research conducted in Africa. It is important to note that adequate resources and infrastructure should accompany the development of regulatory bodies [58]. Governments, funding agencies, and international partners need to allocate sufficient funding to support the establishment and operation of regulatory bodies. This includes providing financial resources for staff salaries, training programs, infrastructure development, and the implementation of monitoring and evaluation systems.

Inter-individual and international partnerships and collaborations are vital in promoting cultural sensitivity and diversity in research. African researchers can benefit from different perspectives, methodologies, and approaches by engaging researchers from diverse backgrounds, disciplines, and countries. These collaborations foster cross-cultural understanding, facilitate knowledge exchange, and encourage incorporating diverse perspectives into research design, data analysis, and interpretation. Consequently, the research findings become more culturally adaptable and applicable to the specific contexts and populations studied. Cultural adaptation of research findings is particularly important in a culturally diverse region such as Africa. It involves tailoring research approaches, interventions, and recommendations to align with the target population's cultural beliefs, values, and practices [30]. This ensures that the research findings are scientifically sound but also acceptable, feasible, and relevant locally. Community participation is vital. Engaging local communities in the research process fosters a sense of ownership, empowers individuals, and ensures that research priorities and methods align with community needs and values. Community members can provide valuable insights, cultural perspectives, and contextual knowledge contributing to the research's cultural sensitivity and relevance. In addition, conducting needs assessments before starting research helps identify specific cultural considerations and tailor research approaches accordingly. This includes understanding local beliefs, social structures, health-care practices, and traditional healing systems. Pilot studies can be conducted to test the feasibility, acceptability, and effectiveness of research interventions within the cultural context. Feedback from pilot studies can inform necessary adaptations and modifications before scaling up research activities.

African translational researchers must prioritize incorporating cultural sensitivity and diversity throughout the research process. This involves awareness of their biases, continuous cultural competency training, and fostering a respectful and inclusive research environment. By embracing diversity and cultural sensitivity, African researchers can contribute to developing more comprehensive and contextually relevant interventions and policies that address unique health challenges.

Enhancing capacity building and retention of skilled resources is vital to strengthening African clinical and translational research. African countries can build sustainable research capacity and foster scientific excellence by investing in developing and retaining a skilled workforce.

Capacity-building initiatives should focus on training and equipping researchers with the necessary knowledge, skills, and competencies to conduct high-quality clinical and translational research. This includes providing comprehensive research training programs, workshops, and mentorship opportunities. By nurturing local talent, African countries can cultivate a pool of qualified researchers who understand the region's unique health-care challenges and cultural context.

Creating an enabling environment that values and supports research careers is essential to retain skilled resources. This involves providing competitive salaries, career advancement opportunities, and supportive work culture. In addition, offering incentives such as research grants, fellowships, and research awards can motivate and recognize the contributions of talented researchers. Partnerships and collaborations with international institutions can also contribute to capacity building and resource retention. African researchers can benefit from the expertise, resources, and networks of international partners through joint research projects,

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knowledge exchange programs, and collaborative mentorship. These collaborations can facilitate skill transfer, exposure to advanced research techniques, and opportunities for publication and career advancement.

Furthermore, establishing research centers of excellence and specialized training programs can help attract and retain skilled resources. These centers can provide state-of-the-art facilities, access to cutting-edge technologies, and a supportive research environment. By creating centers for excellence in specific research areas, African countries can become attractive destinations for skilled researchers within and internationally.

Mentorship programs play a crucial role in capacity building and retention by providing guidance and support to early-career researchers. Established researchers can mentor and nurture the next generation of scientists, fostering their career development and helping them navigates research challenges. Mentorship programs should be structured, offering regular interactions, guidance on research methodology, publication strategies, and career advice. In addition, addressing the brain drain phenomenon requires policies and interventions to incentivize researchers to stay in Africa. This includes providing competitive research funding, facilitating access to research resources, and improving working conditions and infrastructure. Policies should also create opportunities for researchers to contribute to policy development, decision-making processes, and shaping the research agenda in their respective countries.

Partnerships and international collaboration are paramount in advancing African clinical and translational research [59,60]. By collaborating with international organizations, research institutions, and funding agencies, African researchers can benefit from a wide range of opportunities and resources lacking in the local context. These partnerships and collaborations facilitate knowledge exchange, allowing African researchers to gain exposure to advanced methodologies, cutting-edge technologies, and best practices in research. This exposure improves the quality and rigor of African research, promoting scientific excellence and ensuring that research outputs meet international standards. In addition, international collaborations create opportunities for joint research projects that address global health challenges. By pooling their knowledge and resources, researchers from different regions can tackle complex health issues that require multidisciplinary and multi-country approaches. This collaboration enables the development of comprehensive research studies, improves data collection and analysis, and enhances the generalizability of research findings.

Securing financial resources is crucial for supporting research activities in Africa, and partnerships with international funding agencies play a significant role. Many global funding agencies have specific programs and grants supporting research in low- and middle-income countries. By leveraging these opportunities, African researchers can access the necessary funding to conduct high-quality research, invest in research infrastructure, and attract and retain skilled researchers.

Furthermore, international collaborations contribute to research capacity building in Africa. Through mentorship programs, exchange initiatives, and training opportunities, African researchers can acquire new skills, expand their networks, and improve their professional development [16]. This capacity building strengthens the research ecosystem in Africa, fostering a sustainable environment for ongoing research efforts.

Partnerships and collaborations also play a critical role in knowledge translation and dissemination. By working with international partners, African researchers can reach broader audiences, publish their findings in high-impact journals, and share their research with the global scientific community. This increased visibility enhances the reputation of African researchers and raises the profile of research conducted in Africa, leading to greater recognition and opportunities for collaboration. Moreover, partnerships and collaborations foster cultural sensitivity and diversity in research. By engaging with international partners, African researchers can incorporate diverse perspectives, experiences, and cultural considerations into their research design and implementation. This approach ensures that research findings are relevant, applicable, and respectful of the local context and cultural nuances. By embracing cultural sensitivity, researchers can develop more effective interventions tailored to the African population's needs, ultimately leading to improved health outcomes.

5. Limitations and Strengths of the Study

The study presents both limitations and strengths in its analysis. A notable limitation is that the continent's heterogeneity in health-care systems, infrastructure, and socioeconomic conditions may pose challenges in implementing uniform strategies. On the other hand, the study's strengths lie in its evidence-based and actionable recommendations, comprehensive approach encompassing physical infrastructure development, integration of digital health technologies, and capacity building, which enhances the study's credibility and potential for impact. The study offers a holistic perspective on enhancing health-care outcomes in Africa by addressing multiple facets of clinical and translational research.

6. Conclusion

Clinical and translational research in Africa holds immense potential for advancing healthcare and addressing global health inequities. However, several challenges, such as inadequate infrastructure, limited funding, regulatory complexities, restricted access to high-quality healthcare, cultural barriers, and brain drain, hinder the progress of robust research on the continent. To unlock opportunities for advancement, stakeholders must prioritize and invest in African research. This requires increased interest and support from international organizations and collaborations, leveraging the diverse patient populations in the region and nurturing local innovation. By addressing these obstacles and taking advantage of these opportunities, Africa can emerge as a vibrant hub for clinical and translational research, contributing to improved health outcomes and reducing global health disparities. Therefore, it is a call to action for stakeholders to allocate resources and funding to support research in Africa. This commitment is essential not only for the continent's development

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but also for addressing the urgent need to tackle health inequities globally. Investing in clinical and translational research in Africa can drive transformative change, enhance health-care outcomes, and foster a more equitable and sustainable future for all.

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Conflicts of Interest

All authors declare no conflicts of interest.

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