ESCOLA BAHIANA DE MEDICINA E SAÚDE PÚBLICA

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PREVALÊNCIA DOS ESTUDOS ADAPTATIVOS DENTRE AS DIVERSAS ESPECIALIDADES MÉDICAS

TRABALHO DE CONCLUSÃO DE CURSO

SALVADOR - BA

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Trabalho de Conclusão de Curso, apresentado ao curso de graduação em Medicina da Escola Bahiana de Medicina e Saúde Pública, para aprovação parcial no 4° ano do curso de Medicina

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RESUMO

Introdução: Os estudos adaptativos vêm ganhando cada vez mais espaço no meio científico, principalmente, devido a sua maior eficiência propiciada pela maior flexibilidade dos seus métodos. Contudo, devido à essa dinamicidade uma das barreiras desse tipo de estudo tem sido evitar vieses tanto operacionais quanto estatísticos. Justamente por essa complexidade, bem como pelo aumento do número de publicações com metodologia adaptativa, faz-se necessário conhecer o perfil desses estudos até o momento, bem como quais as especialidades que têm conseguido mais utilizar-se dos seus benefícios. **Objetivo:** O presente estudo tem como objetivo descrever a prevalência dos ensaios clínicos adaptativos nas especialidades médicas, bem como identificar os tipos de adaptações mais utilizados e a fase do estudo mais contemplada. **Métodos:** Realizou-se um estudo observacional descritivo de caráter metacientífico, tendo sido realizada uma busca sistemática no banco de dados digital PubMed/MEDLINE em março de 2022, sem limite de tempo, para selecionar os ensaios clínicos randomizados adaptativos. Os dados foram coletados a partir de um formulário pré-estabelecido e analisados com a utilização do software Microsoft Excel. **Resultados:** Na busca inicial, 7.083 artigos identificados, sendo que apenas 150 foram incluídos no estudo. Desses, 94,7% foram publicados a partir de janeiro de 1997. Foi identificado que 26% dos estudos tinham oncologia como especialidade e 45,3% grupo sequencial como adaptação. Ademais, observou-se que 45,3% e 40% dos estudos eram de fase III e II respectivamente, além de que 52% dos estudos apresentaram desfecho positivo com ou sem a presença de spin. **Conclusão:** Observou-se que a maioria dos ensaios clínicos randomizados adaptativos foram publicados a partir de 1997, sendo que grande parte dos estudos incluídos estavam relacionados à área oncológica. Foi identificado que o tipo de adaptação mais utilizado foi o grupo sequencial e os estudos eram predominantemente de fase II e III. Além disso, notou-se que a maioria deles apresentavam desfechos positivos.

Palavras-chave: Ensaio clínico adaptativo. Ensaios clínicos randomizados. Especialidade médica.

ABSTRACT

Introduction: Adaptive studies have been gaining more and more space in the scientific community, mainly due to their greater efficiency provided by the greater flexibility of their methods. However, due to this dynamism, one of the barriers of this type of study has been avoiding both operational and statistical biases. Precisely because of this complexity, as well as the increase in the number of publications with adaptive methodology, it is necessary to know the profile of these studies so far, as well as which specialties have managed to make the most use of their benefits. **Objectives:** The present study aims to describe the prevalence of adaptive clinical trials in medical specialties, as well as to identify the most used types of adaptations and the most contemplated phase of the study. **Methods:** A meta-scientific descriptive observational study was carried out, with a systematic search in the PubMed/MEDLINE digital database in March 2022, with no time limit, to select adaptive randomized clinical trials. Data were collected from a pre-established form and analyzed using Microsoft Excel software. **Results:** In the initial search, 7,083 articles were identified, of which only 150 were included in the study. Of these, 94.7% were published from January 1997 onwards. It was identified that 26% of the studies had oncology as a specialty and 45.3% had a sequential group as an adaptation. Furthermore, it was observed that 45.3% and 40% of the studies were phase III and II respectively, in addition to the fact that 52% of the studies had a positive outcome with or without presence of spin. **Conclusion:** It was observed that most adaptive randomized clinical trials were published from 1997 onwards, and most of the included studies were related to the oncology area. It was identified that the most used type of adaptation was the sequential group, and the studies were predominantly phase II and III. Furthermore, it was noted that most of them had positive outcomes.

Keywords: Adaptive clinical trial. Medical specialty. Randomized clinical trials.

SUMÁRIO

1 INTRODUÇÃO

Os Ensaios Clínicos Randomizados (ECRs) consistem em uns dos principais meios para a obtenção de informações baseadas em evidências que moldam a prática em saúde atualmente, sendo considerados o padrão ouro do conhecimento médico.[1,2]

Esse tipo de estudo é definido como um experimento científico prospectivo com envolvimento de seres humanos no qual uma intervenção terapêutica será avaliada, sendo cada participante designado aleatoriamente a receber um tratamento específico.[3] Contudo, apesar dessa relevância e aplicabilidade, os ECRs possuem as suas limitações, visto que, gradativamente, foram demandando cada vez mais um apoio substancial para serem realizados.[2]

Nesse sentido, os estudos adaptativos têm sido uma alternativa para contornar esses contratempos, pois, quando utilizados adequadamente, tem o potencial de reduzir a alocação de recursos, diminuir o tempo para conclusão do estudo e/ou aumentar as chances de sucesso de um estudo. Portanto, costumam ser mais eficientes, informativos e éticos do que ensaios clínicos com desenhos fixos. Isso se deve à possibilidade de flexibilização dos métodos inerente a esses estudos, ou seja, eles permitem que sejam feitas modificações após o seu início que foram previamente planejadas e descritas no seu protocolo.[4,5]

Dentre as formas de adaptações usadas nesses estudos, tem-se, por exemplo, ajustes no tamanho amostral para garantir o poder adequado, mudança na proporção de alocação para tratamentos mais promissores ou informativos, alterações nas doses para alocar mais pacientes para o tratamento de interesse, entre outras.[4,6]

Ultimamente, tem-se observado um aumento no uso dos estudos adaptativos publicados por pesquisadores de todo o mundo, sobrepondo os ECRs em diversos cenários, destacando-se, principalmente, o seu uso na área de oncologia.[7] Dessa forma, o objetivo desse estudo consiste em descrever em quais áreas de especialidade médica os estudos adaptativos têm sido mais utilizados com uma discussão sobre as razões para essa possível predileção, bem como identificar os tipos de adaptações mais utilizados e em quais fases do estudo as adaptações costumam ser mais exploradas.

2 OBJETIVO

2.1 Geral

- Descrever a prevalência dos ensaios clínicos adaptativos dentre as especialidades médicas.

2.2 Específicos

- Apresentar os tipos de adaptações mais utilizados nos ensaios clínicos adaptativos, bem como a sua prevalência.
- Caracterizar as fases do estudo dos ensaios clínicos adaptativos.

3 REVISÃO DE LITERATURA

Para guiar a prática clínica, os Ensaios Clínicos Randomizados (ECRs) são considerados as melhores ferramentas, visando, principalmente, avaliar intervenções em saúde, sejam elas medicamentosas ou não.[8] Nesse sentido, seu uso é considerado quando há incerteza sobre o efeito de uma exposição ou tratamento e quando a exposição pode ser modificada no estudo.[9]

Geralmente, os ECRs podem ser divididos em fases na pesquisa para determinar se uma intervenção seria benéfica ou prejudicial. Na fase I é verificado principalmente se o tratamento é seguro. Geralmente, nessa etapa são avaliadas a tolerabilidade, a farmacocinética e a farmacodinâmica. Os estudos de fase II por sua vez, visam avaliar a eficácia potencial de determinada intervenção, caracterizando o seu benefício de forma convincente. A "fase de pré-comercialização", fase III, objetiva realizar uma avaliação completa do tratamento, sendo projetadas para comparar a eficácia de uma nova terapêutica com a terapêutica padrão. Por fim, os estudos na fase IV iram focar em como a intervenção vem funcionando no mundo real a longo prazo, por isso, são também chamados de "estudos pós comercialização".[10,11]

Apesar da sua grande importância e utilidade clínica, os ECRs têm demonstrado cada vez mais limitações para a sua execução nos últimos anos. Hoje, existe um extenso processo burocrático e corporativo para realização desses estudos, tornando-os dependente de uma infraestrutura dispendiosa para a formulação do design de pesquisa, a realização do atendimento ao paciente, a manutenção dos registros, bem como a execução da revisão ética e da análise estatística.[2]

Nesse cenário, os estudos adaptativos têm sido desenvolvidos com o intuito de fornecer substratos metodológicos para minimizar essas adversidades e, por isso, vêm sendo cada vez mais utilizados por pesquisadores de todo o mundo.[7]

Segundo os critérios da *Food and Drug Administration* (FDA), um estudo é dito adaptativo quando permite modificações planejadas prospectivamente com base no acúmulo de dados obtidos pelo estudo, sem que ocorra prejuízos à integridade e à validade dele, sendo que para que isso aconteça, essas alterações devem ser planejadas e descritas no protocolo do ensaio clínico antes que ele tenha início.[12] Ou seja, os resultados dos pacientes são observados e analisados em pontos intermediários predefinidos e modificações predeterminadas no desenho do estudo podem ser implementadas com base nessas observações.[7]

Existem diversas formas de adaptação que podem ser utilizadas, como, por exemplo, adaptação da faixa de dosagem, randomização adaptativa, grupo sequencial, adaptação por biomarcadores, *pick the winner/drop the loser*, enriquecimento da população.[5,6]

Segundo a revisão de literatura feita por Bothwell et al. utilizando 142 trabalhos, o tipo de adaptação mais utilizado foram os estudos integrados de fase II/III, seguidos pelos estudos de grupos sequenciais.[7] Em outra revisão feita por Cerqueira et al. com 78 artigos, os estudos integrados de fase II/III também foram os com maior destaque, seguidos pelos de adaptações de faixa de dosagem e pelos *pick the winner/drop the loser*.[13]

Nessa perspectiva, é visível que uma das formas de adaptação mais utilizadas consiste nos estudos integrados de fase II/III. Esses desenhos permitem tanto a seleção de tratamento ou dose em uma análise provisória, quanto a avaliação comparativa da eficácia com controle no mesmo estudo, o que possibilita uma minimização do atraso de tempo entre as fases II e III.[14] Contudo, esse projeto adaptativo é considerado menos bem compreendido e pode introduzir viés, sendo que a taxa do erro tipo I pode ser maior do que a indicada, o que acaba se tornando um motivo de preocupação.[5,6] Existem ainda estudos de fase I/II e I/II/III. Naqueles de fase I/II, busca-se determinar a dose que maximiza o efeito terapêutico e minimiza os efeitos adversos. Já nos ensaios de I/II/III, em duas etapas contínuas, I-II, é feita uma otimização de dosagem, baseando-se no binário eficácia e toxicidade, o que permite uma transição direta de uma adaptação de dose para uma comparação randomizada com um grupo controle em um estudo de fase III confirmatório, assumindo-se que uma dose ideal possa ser estimada a partir do estágio I-II.[15]

Os estudos adaptativos com grupos sequenciais também têm sido usados por muitos anos pela comunidade de estudos estatísticos e clínicos. Eles permitem uma análise interina dos resultados por grupo de tratamento, o que possibilita uma interrupção precoce em caso de sucesso ou futilidade. Justamente por isso, uma desvantagem desse tipo de estudo consiste na incerteza do que os dados acumulados podem demonstrar, podendo tanto tornar necessário o envolvimento de toda a coorte, como também indicar a necessidade do estudo ser interrompido precocemente.[5]

Já nos projetos com adaptações de faixa de dosagem, por sua vez, os pacientes são alocados para receber múltiplas doses de tratamento. Em análises intermediárias, o desenho do estudo é adaptado para alocar mais pacientes às doses de tratamento de interesse, reduzindo a alocação

para as doses que demonstraram ser menos eficazes, podendo ocorrer descontinuação desses subgrupos, como também é possível a interrupção precoce de todo o estudo.[13,16]

Outra das formas de adaptações mais utilizadas são os estudos *pick the winner/drop the loser*, em que é possível o abandono de grupos de tratamento inferior, a modificação dos braços de tratamento e a possível adição de novos braços com base na revisão dos dados acumulados na análise interina.[7]

Tanto os estudos com adaptações de faixa de dosagem quanto os com design *pick the winner/drop the loser* são principalmente utilizados em estudos exploratórios ou de fase inicial com o objetivo de obter informações para projetar estudos subsequentes.[6]

Além disso, existem estudos que se utilizam de mais de um tipo de adaptação, geralmente atrelando em só estudo adaptações de grupo sequencial com estudos integrados e "*drop the losers"*, ou adaptações na faixa de dosagem com randomização adaptativa.[17]

Nesse sentido, é importante ressaltar que existem maiores dificuldades no planejamento, financiamento e interpretação dos dados em um estudo adaptativo. Ou seja, ainda que apresentem maior flexibilidade, as alterações no projeto e o tempo de análise intermediária dos dados devem não só ser planejados previamente, mas também devem ser avaliados por formas pré-estabelecidas com o intuito de evitar tanto vieses operacionais quanto estatísticos.[5,6]

Nesse sentido, a observação de um dos pontos mais importantes acerca da confiabilidade dos resultados apresentados em ensaios clínicos em geral, o *spin*, faz-se igualmente necessária nos estudos com adaptações. Existem inúmeras maneiras em que ele se faz presente nas pesquisas médicas, mas, em essência, consiste em uma tentativa de embelezar ou omitir resultados desfavoráveis. Nessa prática, os autores do estudo podem, por exemplo, ocultar resultados de toxicidade ou apresentar de forma seletiva desfechos com base na significância estática.[18,19]

Por esses motivos, os comitês de monitoramento de dados (CMD) possuem ainda mais importância em ensaios adaptativos. Esses comitês detêm a função de monitorar os dados acumulados, garantir a segurança dos participantes do estudo, analisar o andamento do projeto, desempenhando um papel importante na decisão da implementação de adaptações planejadas primariamente nas análises intermediárias. Ou seja, eles consistem em grupos de especialistas que visam basicamente a proteção dos pacientes e a garantia da manutenção da integridade científica do estudo.[20]

Os CMDs geralmente são requisitados em ensaios clínicos adaptativos em que há a presença de uma doença ou de condições que ameacem a vida e/ou em projetos em que o plano de adaptação previsto irá revelar ao patrocinador o efeito do tratamento durante a condução do estudo.[21] Para que desempenhem bem suas responsabilidades, seus membros necessitam ter pleno conhecimento das implicações de uma adaptação além de, preferencialmente, terem experiência em fazer o tipo de decisão adaptativa proposto por determinado desenho.[20]

Dessa forma, fica visível que o uso de ensaios adaptativos é crescente nos últimos anos e, apesar de oferecerem vantagens em relação aos ECRs não adaptativos, ainda possuem suas limitações e, por esse motivo, mecanismos como os CMDs vêm sendo aprimorados para minimizar o seu risco de viés e promover a manutenção da sua integridade científica.

4 MÉTODOS

4.1 Desenho de estudo

Trata-se de um estudo observacional descritivo de caráter metacientífico realizado no ano de 2022.

4.2 Estratégia de busca

Foi conduzida uma busca sistemática no banco de dados digital do PubMed/MEDLINE em março de 2022, sem limite de tempo, considerando os verbetes mais utilizados para descrever o desenho adaptativo, a partir dos descritores obtidos no Medical Subjet Headings (MeSH). Os descritores utilizados foram: "Adaptive Clinical Trial" OR "adaptive hypothesis" OR "adaptive treatment" OR "biomarker adaptive" OR "adaptive dose-finding" OR "pick-the-winner" OR "drop-the-loser" OR "sample size reassessment" OR "sample size re-estimation" OR "adaptive randomization" OR "group sequential" OR "multiple adaptive" OR "Bayesian sample size" OR "adaptive group sequential" OR "adaptive seamless" OR "multiple adaptive" OR "group sequential" OR "sample size reassessment" OR "group sequential design" OR "adaptive enrichment" OR "seamless studies" OR “seamless”

4.3 Elegibilidade

4.3.1 Critérios de Inclusão

Foram incluídos apenas ensaios clínicos randomizados de desenho adaptativo de fases II, II/III, III ou IV, com seres humanos, seguindo os critérios da Food and Drug Administration (FDA), que testam intervenções médicas, publicados na língua inglesa.

4.3.2 Critérios de Exclusão

Foram excluídos estudos que não envolvem intervenções em humanos, revisões sistemáticas, meta-análises, abstracts, comentários, métodos estatísticos ou discussões econômicas. Além disso, foram excluídos estudos em fase I e seamless fase I/II visto que esses modelos vão ter um baixo impacto na aprovação e utilização de tratamento. Também foram excluídos artigos que não estejam disponíveis na língua inglesa e que não estejam de acordo com os critérios da FDA.

4.4 Identificação e seleção de estudos

Quatro membros fizeram, separadamente, a busca dos artigos encontrados na base de dados digitais. Um quinto membro ficou responsável pela busca dos artigos não encontrados nessa primeira busca, entrando em contato com os autores através de e-mail. Na etapa seguinte, foi feita uma leitura completa dos artigos encontrados e seleção dos artigos que elegíveis a partir dos critérios de inclusão e a remoção dos que não fizeram parte dos critérios desejados.

4.5 Variáveis do estudo

Foram analisadas as seguintes variáveis:

I. Especialidade médica, classificada em: Oncologia; Medicina Intensiva; Imunologia; Ortopedia; Reumatologia; Gastroenterologia; Dermatologia; Otorrinolaringologia; Anestesiologia e dor; Ginecologia/Obstetrícia; Hematologia; Pediatria; Cuidados paliativos; Cardiologia; Psiquiatria; Medicina Geral ou Medicina da Família e Comunidade; Endocrinologia; Pneumologia; Nefrologia; Infectologia; Neurologia; Cirurgia geral ou subespecialidade da CG.

II. Desfecho do estudo, classificado em: Positivo sem spin; negativo sem spin; positivo com spin; negativo com spin; inconclusivo.

III. Tipo de adaptação, classificado em: Randomização adaptativa, múltiplas adaptações, estudos integrados, grupo sequencial, adaptação de faixa de dosagem, *pick the winner/drop the loser*, adaptação por biomarcadores, adaptação bayseiana, reavaliação do tamanho amostral, não identificável.

4.6 Análise estatística

A análise dos dados coletados, a criação das tabelas e gráficos, bem como os possíveis cálculos necessários serão feitos utilizando o programa Microsoft Excel.

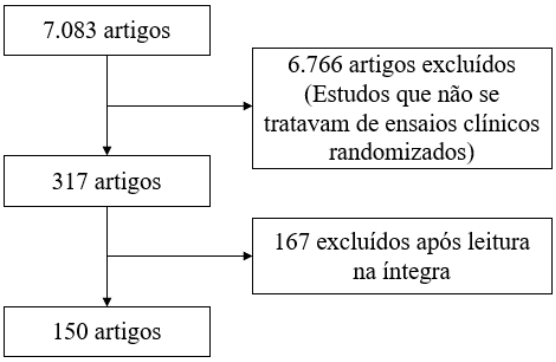
4.7 Aspectos éticos

Por tratar-se de uma revisão sistemática, não há necessidade de submissão ao Comitê de Ética em Pesquisa.

5 RESULTADOS

A partir da busca na base de dados PubMed/MEDLINE, utilizando os descritores supracitados, foram encontrados 7.083 artigos, dos quais 6.766 foram excluídos por não se adequarem aos critérios de elegibilidade. Dessa forma, 317 foram lidos na íntegra, sendo 167 artigos excluídos devido não adequação aos critérios de elegibilidade, sendo incluídos no estudo o total de 150 artigos (Figura 1).

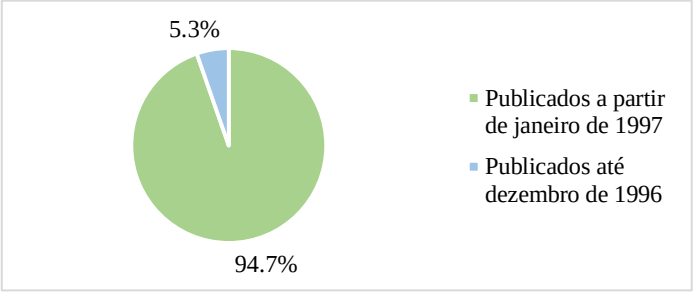
Figura 1 – Fluxograma de seleção dos estudos



Fonte: Criação do próprio autor

Como pode ser observado na Figura 2, dos 150 artigos incluídos, 5,3% foram publicados até dezembro de 1996 e 94,7% foram publicados a partir de janeiro de 1997 (Apêndice A – Lista dos artigos incluídos).

Figura 2 – Distribuição dos artigos por data de publicação

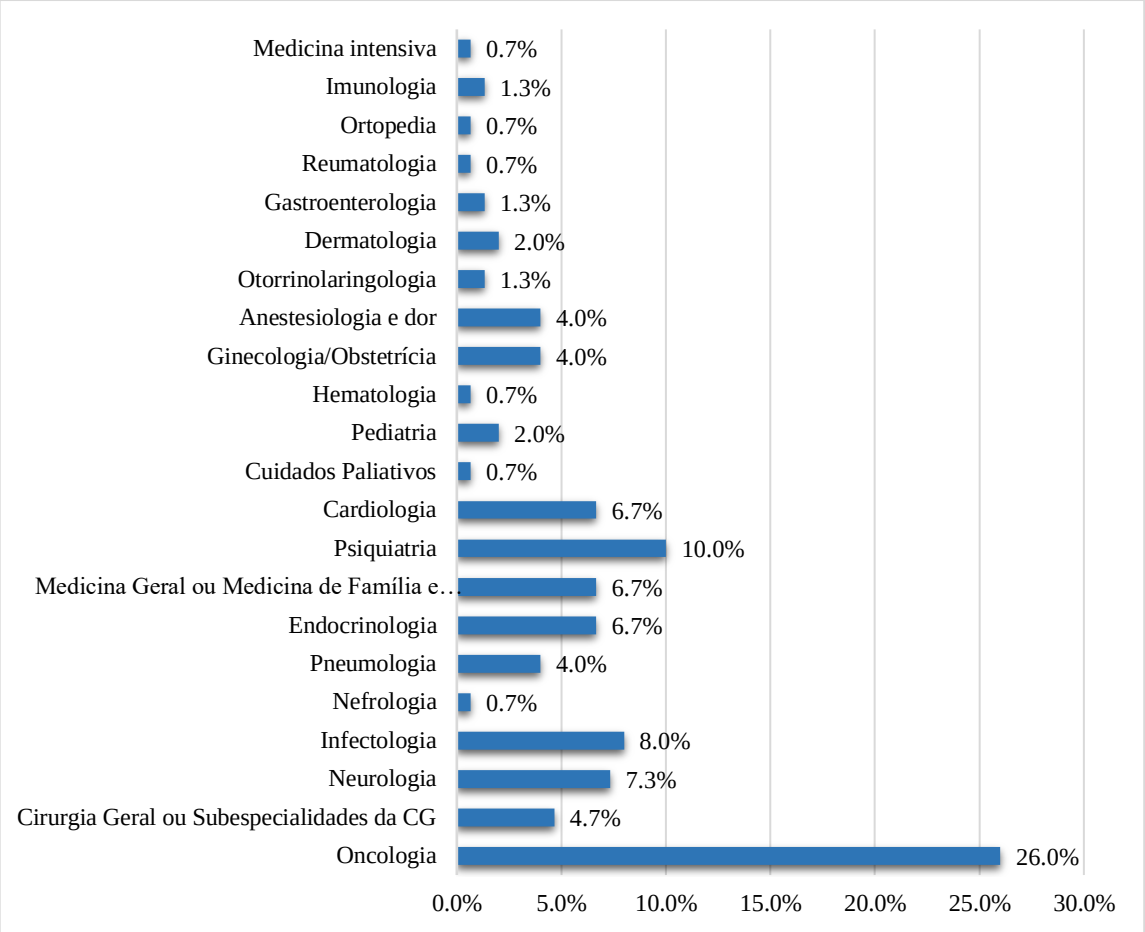


Fonte: Criação do próprio autor

5.1 Perfil dos artigos

Dos artigos incluídos, observou-se um predomínio do uso de desenhos adaptativos na área da Oncologia (26%), seguida, respectivamente, pelas áreas da Psiquiatria (10%), Infectologia (8%), Neurologia (7,3%), Endocrinologia (6,7%), Cardiologia (6,7%), Medicina geral ou Medicina da Família e Comunidade (6,7%) (Figura 3).

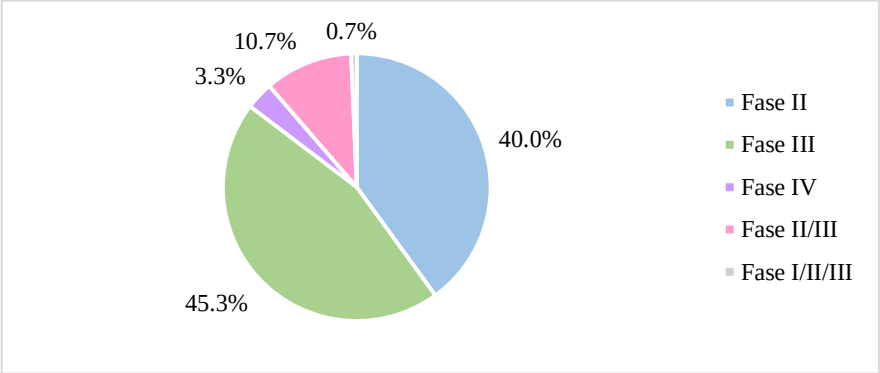
Figura 3 – Distribuição dos artigos incluídos por especialidade médica.



Fonte: Criação do próprio autor

Quanto ao estágio dos estudos, 0,7% eram de fase I/II/III; 40% eram de fase II; 10,7% eram de fase II/III; 45,3% eram de fase III; e 3,3% eram estudos de fase IV (Figura 4).

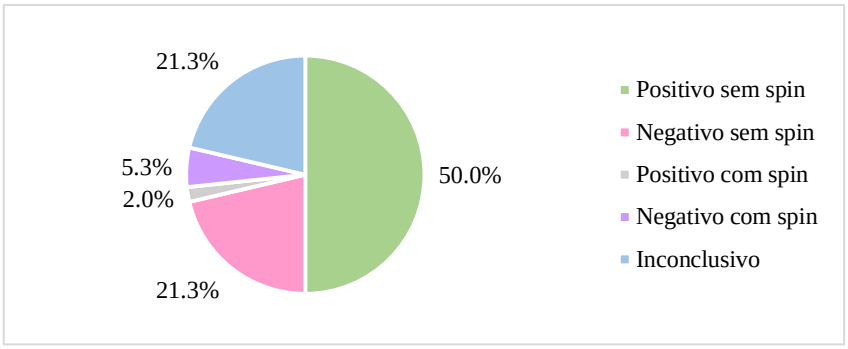
Figura 4 – Distribuição dos artigos incluídos por etapa de pesquisa.



Fonte: Criação do próprio autor

Quanto a conclusão dos estudos, 50% apresentaram desfechos positivos sem spin, 2% positivos com spin, 21,3% negativos sem spin, 5,3% negativos com spin e em 21,3% ele foi inconclusivo (Figura 5).

Figura 5 – Distribuição dos artigos incluídos de acordo com o desfecho.

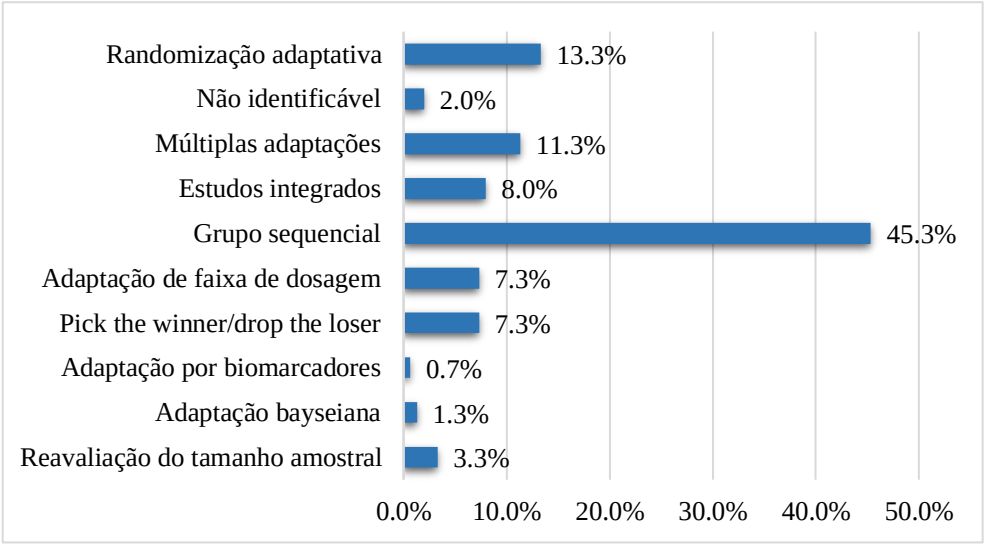


Fonte: Criação do próprio autor

5.2 Tipos de Adaptações

O tipo de adaptação mais utilizado foi o grupo sequencial (45,3%), seguido pelos estudos com randomização adaptativa (13,3%) e múltiplas adaptações (11,3%). Dentro da amostra, 7,9% eram estudos integrados (Fase II/III), 7,3% utilizaram adaptação de faixa de dosagem, 7,3% usaram o método adaptativo *Pick-the-winner/drop-the-loser*, 3,3% utilizaram o método adaptativo reavaliação do tamanho amostral, 1,3% adaptação bayesiana e 0,7% adaptação por biomarcadores. Em 2% dos estudos o tipo de adaptação não foi identificável (Figura 6).

Figura 6 – Distribuição dos artigos incluídos por tipo de adaptação.



Fonte: Criação do próprio autor

6 DISCUSSÃO

O presente estudo visou descrever a prevalência dos ensaios clínicos adaptativos nas especialidades médicas, identificando em quais as fases de estudo eles têm sido aplicados, bem como detectar os tipos de adaptações mais utilizados.

Foi observado que 94,7% dos artigos incluídos foram publicados a partir de janeiro de 1997, o que corrobora com a percepção de que uso dessa forma de pesquisa começou a se difundir só recentemente, tendo seu número aumentado expressivamente a partir desse marco temporal.[7] Esse crescimento pode ser explicado pelo fato de os ensaios adaptativos possibilitarem não só uma redução no tempo de conclusão e do número de pacientes expostos a intervenções inferiores, mas também a uma melhor probabilidade de se detectar os efeitos de determinado tratamento.[22]

O presente trabalho evidenciou que oncologia concentra a maior parcela dos ensaios clínicos randomizados adaptativos, cerca de 26% dos estudos. Esse achado pode ter relação com inúmeros fatores. Partindo do pressuposto que um estudo pode levar anos para chegar a um reposta definitiva, especialmente, com base na sobrevida dos pacientes, é razoável inferir que a comunidade científica esteja mais disposta a tomar decisões sobre o tratamento com base em desfechos provisórios no cenário da oncologia, o que ratificaria o conceito de ensaio adaptativo da FDA.[5,23] Além disso, nos casos em que existam, por exemplo, limitações no tratamento para um determinado tipo de câncer, as adaptações tem o potencial de otimizar e acelerar a obtenção de um novo tratamento que seja promissor para que os pacientes com essa enfermidade possam ter acesso.[23]

Esses achados corroboram com aqueles encontrados em outras estudos similares. Na revisão de literatura de Bothwell et al. dos 142 ensaios clínicos adaptativos analisados, 28 eram na área da oncologia, ao mesmo tempo em que na revisão de Cerqueira et al. esse número foi de 21 nos 78 trabalhos incluídos.[7,13]

Ainda que os estudos adaptativos sejam mais utilizados na área oncológica, eles mostraram-se presentes em diversas áreas terapêuticas. Destacaram-se as áreas da Psiquiatria (10%), Infectologia (8%), Neurologia (7,3%), Endocrinologia (6,7%), Cardiologia (6,7%), Medicina geral ou Medicina da Família e Comunidade (6,7%).

Foi identificado que cerca de 45% e 40% dos estudos eram de fase III e II respectivamente, o que, possivelmente, ocorre em função dessas duas etapas da pesquisa possuírem um caráter tanto exploratório quanto confirmatório.[24,25] Nesse sentido, é coerente inferir que projetos que oferecem um maior valor de informação por unidade de recurso investida tornam-se ainda mais vantajosos.[26]

Além disso, nesse estudo, observou-se que o tipo de adaptação mais utilizado foi o grupo sequencial, 45,3%, seguido pelos estudos de randomização adaptativa, 13,3%, e múltiplas adaptações, 11,3%. O primeiro possibilita que seja feita uma análise interina dos resultados por grupo de tratamento, viabilizando uma interrupção precoce tanto em caso de sucesso quanto de futilidade.[5] No caso da randomização adaptativa, ela permite que, através da análise intermediária dos resultados, o esquema de randomização seja ajustado para que os pacientes inscritos posteriormente no estudo tenham maior probabilidade de serem randomizados para o braço de tratamento que vem se mostrando mais eficaz.[7] Por sua vez, o termo múltiplas adaptações é compreendido como a junção de uma ou mais formas de adaptação em um mesmo estudo, o que dificulta mais a inferência estatística.[27]

Tais achados não corroboram completamente com aqueles encontrados em estudos similares. Na revisão de literatura feita por Bothwell et al. o tipo de adaptação mais utilizado foram os estudos integrados de fase II/III, seguidos pelos estudos de grupos sequenciais.[7] Já na revisão feita de Cerqueira et al., os estudos integrados de fase II/III tiveram maior destaque, seguidos pelos de adaptações de faixa de dosagem e pelos *pick the winner/drop the loser*.[13]

Ademais, dos artigos incluídos, 52% apresentaram desfechos positivos e 26,6% desfechos negativos. Esse achado corrobora com aqueles encontrados na literatura de que existe uma tendência a não publicação de resultados negativos, ou seja, ensaios clínicos de novos medicamentos, por exemplo, que não apresentam efeitos estatisticamente significativos são menos propensos a serem apresentados em reuniões, enviados para publicação, recomendados para publicação por revisores ou selecionados para publicação por editores do que os ensaios que mostram diferenças estatisticamente significativas.[28,29]

Por fim, esse trabalho apresentou como principal limitação a dificuldade de inclusão de todos os ensaios clínicos randomizados adaptativos até março de 2022, devido à falta de descritores relacionados a esse tipo de estudo na base de dados utilizada, principalmente no que diz respeito à ausência de declaração de adaptação tanto no título e quanto no resumo de muitos artigos.

Ademais, apesar das definições já existentes, a delimitação do que define um artigo como adaptativo ainda é um ponto de discussão, o que pode ter levado a exclusão de artigos que não deixavam claras as adaptações na sua metodologia.

7 CONCLUSÃO

De acordo com os resultados coletados e analisados nesse estudo foi possível observar que houve um aumento expressivo dos estudos adaptativos a partir do ano de 1997, sendo identificado que os ensaios clínicos randomizados adaptativos são mais utilizados na área oncológica e o tipo de adaptação mais contemplado foi o grupo sequencial. Além disso, verificou-se que nessa amostra os trabalhos apresentavam na sua maioria desfechos positivos, com ou sem a presença de spin, e eram predominantemente de fase III e II respectivamente.

Por fim, nota-se que, com o incremento recente no número de estudos adaptativos, é razoável esperar que o olhar da comunidade científica no geral esteja consciente não só da existência desse tipo de trabalho, mas também da forma como eles funcionam e o que eles propõem. Por esse motivo, o presente estudo visou traçar um perfil dos ensaios clínicos randomizados adaptativos até março de 2022, com ênfase em quais as especialidades médicas que mais vêm se apropriando dessa ferramenta.

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APÊNDICE A – Lista dos artigos incluídos

Título	Primeiro autor	Ano de publicação	Jornal de publicação
Biomarker-adaptive threshold design: a procedure for evaluating treatment with possible biomarker-defined subset effect[30]	Wenyu Jiang	2007	JNCI: Journal of the National Cancer Institute
Adaptive Randomization of Neratinib in Early Breast Cancer[31]	John W. Park	2016	The new england journal of medicine
Proof of Concept for an Adaptive Treatment Strategy to Prevent Failures in Internet-Delivered CBT: A Single-Blind Randomized Clinical Trial With Insomnia Patients[32]	Erik Forsell	2019	The American Journal of Psychiatry
Efficacy and Safety of Seltorexant as Adjunctive Therapy in Major Depressive Disorder: A Phase 2b, Randomized, Placebo-Controlled, Adaptive Dose-Finding Study[33]	Adam Savitz	2021	International Journal of Neuropsychopharmacology
Rationale and design of the Study To Understand Fall Reduction and Vitamin D in You (STURDY): A randomized clinical trial of Vitamin D supplement doses for the prevention of falls in older adults[34]	Erin D Michos	2018	Contemporary Clinical Trials
ESCAschool study: trial protocol of an adaptive treatment approach for school-age children with ADHD including two randomised trials[35]	Manfred Döpfner	2017	BMC Psychiatry
A multi-centre, randomised, double-blind, placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study)[36]	Ulrich Hegerl	2017	European Neuropsychopharmacology

Acute treatment of migraine with the selective 5-HT1F receptor agonist lasmiditan--a randomised proof-of-concept trial[37]	Michel D Ferrari	2010	Cephalalgia
Adolescents with cannabis use disorders: Adaptive treatment for poor responders[38]	Yifrah Kaminer	2017	Addictive Behaviors
Dose-finding results in an adaptive, seamless, randomized trial of once-weekly dulaglutide combined with metformin in type 2 diabetes patients (AWARD-5)[39]	Z Skrivanek	2014	Diabetes Obesity and Metabolism
Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods[40]	Tudor G Jovin	2017	International Journal of Stroke
Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): Methodology of a pragmatic, response-adaptive, prospective randomized clinical trial[41]	Benjamin T King	2019	International Journal of Stroke
The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study[42]	Alexis Mitelpunkt	2019	Epilepsy & Behavior
Extended treatment for cigarette smoking cessation: a randomized control trial[43]	Jennifer R Laude	2017	Addiction
TBCRC023: A Randomized Phase II Neoadjuvant Trial of Lapatinib Plus Trastuzumab Without Chemotherapy for 12 versus 24 Weeks in Patients with	Mothaffar F Rimawi	2020	Clinical Cancer Research

HER2-Positive Breast Cancer[44]			
Efficacy of Losartan in the management of Post-Dialysis Euvolemic Hypertension (HELD-Trial): A Single-Blind Randomized Control Trial[45]	Raja Ahsan Aftab	2016	Scientific Reports
A genotype-directed comparative effectiveness trial of Bucindolol and metoprolol succinate for prevention of symptomatic atrial fibrillation/atrial flutter in patients with heart failure: Rationale and design of the GENETIC-AF trial[46]	Jonathan P Piccini	2018	American Heart Journal
Covariate-adjusted adaptive randomization in a sarcoma trial with multi-stage treatments[47]	Peter F Thall	2005	Statistics in Medicine
Pharmacokinetic interaction between the CYP3A4 inhibitor ketoconazole and the hormone drospirenone in combination with ethinylestradiol or estradiol[48]	Herbert Wiesinger	2015	British Journal of Clinical Pharmacology
Low dose dexamethasone as treatment for women with heavy menstrual bleeding: A response-adaptive randomised placebo-controlled dose-finding parallel group trial (DexFEM)[49]	Pamela Warner	2021	EBioMedicine
Conjunctival autograft alone or combined with adjuvant beta-radiation? A randomized clinical trial[50]	Gustavo Arruda Viani	2012	International Journal of Radiation Oncology, Biology, Physics

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