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The Evolution, Methodology, and Epistemological Value of Clinical Case Reports in Contemporary Evidence-Based Medicine

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ABSTRACT

Aims: To evaluate the structural evolution, methodological rigor, and reporting compliance of clinical and medical case reports following the introduction of the Consensus-based Clinical Case Reporting (CARE) guidelines, and to establish a standardized framework for authoring high-impact case reports.

Methods: A retrospective bibliometric and methodological audit was performed on 450 peer-reviewed clinical case reports indexed in PubMed/MEDLINE, Embase, and the Directory of Open Access Journals between 2010 and 2025. Manuscripts were stratified into pre-guideline (2010–2013, n = 150) and post-guideline (2014–2025, n = 300) cohorts and independently scored against a 30-item rubric spanning all 13 CARE checklist domains.

Results: Post-guideline manuscripts achieved significantly higher normalized compliance scores than pre-guideline reports (78.4% ± 11.2% vs. 54.1% ± 14.6%, $p < 0.001$), with progressive gains from early (2014–2019: 73.8%) to mature adoption (2020–2025: 83.0%). Journals mandating CARE checklists demonstrated superior compliance (85.6% vs. 69.2%, $p < 0.001$). Major improvements occurred in chronological timelines (18.0% to 64.7%), written informed consent (42.0% to 89.3%), and follow-up adverse event documentation (39.3% to 71.7%), whereas patient perspectives (14.3%) and differential diagnostic reasoning (51.0%) remained underreported.

Conclusion: Standardized reporting guidelines substantially enhance the transparency and reproducibility of clinical case reports. Integrating chronological timelines, reference-anchored diagnostics, objective causality assessment, ethical anonymization, and patient perspectives ensures individual clinical observations effectively advance pharmacovigilance, rare disease characterization, and precision medicine.

Keywords: Case Reports; Evidence-Based Medicine; Reporting Guidelines; Pharmacovigilance; Diagnostic Reasoning.

1. INTRODUCTION

Across every empirical discipline—from astrophysics and evolutionary biology to clinical medicine and pharmacology—scientific progress depends on a continuous dialogue between two complementary modes of

inquiry: population-level generalization and the close examination of singular, anomalous phenomena. While large-scale statistical studies establish universal laws and average behavioral patterns, unexpected anomalies observed in individual subjects frequently expose hidden mechanisms, challenge prevailing theoretical paradigms, and spark entirely new lines of investigation. In the biomedical and health sciences, the formal vehicle for capturing and disseminating these singular human observations is the clinical and medical case report. Serving as the oldest continuous genre of scientific communication—with roots stretching from the ancient Egyptian Edwin Smith Papyrus (circa 1600 BCE) and Hippocratic treatises to the foundational clinico-pathological monographs of Thomas Sydenham, Giovanni Battista Morgagni, and Sir William Osler [1,2]—the case report has historically functioned as the primary bedside radar for medical discovery.

A substantial body of historical and bibliometric literature underscores the transformative impact of well-documented single-patient observations on global public health and translational science. Landmark clinical breakthroughs—including James Parkinson's 1817 characterization of paralysis agitans[3], the early recognition of thalidomide-induced phocomelia in the 1960s, and the 1981 identification of Acquired Immunodeficiency Syndrome (AIDS) through five unusual cases of Pneumocystis carinii pneumonia [4]—all originated as granular clinical case descriptions. Subsequent empirical analyses of high-impact general medical periodicals by Vandenbroucke (2001) [5], Albrecht et al. (2005) [6], and Aronson and Hauben (2006) [7] demonstrated that case reports and small case series disproportionately drive early pharmacovigilance signal detection, uncover rare genetic and infectious pathologies [8]), and generate mechanistic hypotheses that later justify resource-intensive clinical trials. Furthermore, educational scholars such as Jenicek (2001) [9] and Bowen (2006) [10] have highlighted their enduring pedagogical value in modeling diagnostic reasoning, cognitive debiasing, and complex decision-making under uncertainty for trainees across healthcare and allied life sciences.

Despite this rich scientific pedigree, the late twentieth-century rise of Evidence-Based Medicine (EBM) fundamentally reshaped the epistemological hierarchy of biomedical research (Evidence-Based Medicine Working Group, 1992 [11]). As randomized controlled trials (RCTs), systematic reviews, and large-scale observational cohorts ascended to the apex of evidence pyramids due to their statistical power and internal validity (Murad et al., 2016 [12]), single-patient reports were increasingly marginalized as 'anecdotal evidence.' Concurrently, bibliometric pressures surrounding Journal Impact Factors led several prominent medical periodicals to curtail case report sections, while empirical quality audits—such as those by Kaszkin-Bettag and Hildebrandt (2012) [13] and Rison (2013) [14]—exposed widespread methodological deficiencies in published reports, including disorganized chronologies, omitted diagnostic reference ranges, lack of objective causality scoring, and inconsistent documentation of patient informed consent. Yet, as Rothwell (2005) [15] and Lillie et al. (2011) [16] have argued, population-based trials rely on strict eligibility criteria that routinely exclude older adults, pregnant individuals, pediatric cohorts, and patients with complex multimorbidities or unique pharmacogenomic profiles—leaving an urgent epistemological gap that only rigorous 'n-of-1' clinical reporting can bridge.

To address these reporting inconsistencies and restore scientific credibility to single-patient observations, an international consortium of clinicians, epidemiologists, and journal editors introduced the Consensus-based Clinical Case Reporting (CARE) guidelines in 2013 (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]). Modeled

after the CONSORT and PRISMA frameworks, CARE established a structured, 13-domain reporting standard designed to maximize transparency and reproducibility. However, more than a decade after its publication, critical questions remain regarding the real-world adoption of these guidelines across diverse biomedical specialties, the specific impact of mandatory editorial checklist enforcement, and the persistence of blind spots in clinical reasoning and patient-centered reporting (Nissen and Wynn, 2014 [19]).

Accordingly, the present study establishes a rigorous, dual-purpose investigation designed to resonate with clinicians, pharmacologists, biostatisticians, methodologists, and biomedical editors alike. First, we conduct a comprehensive, 15-year retrospective bibliometric and methodological audit of 450 peer-reviewed clinical case reports published between 2010 and 2025, quantitatively comparing reporting rigor across pre-guideline (2010–2013) and post-guideline (2014–2025) eras using a validated 30-item CARE compliance rubric (Table S1). Second, leveraging the empirical deficiencies identified in our audit, we propose an integrated, end-to-end methodological solution and standardized operational toolkit—encompassing a four-phase publication workflow, reference-anchored diagnostic benchmarks, objective pharmacovigilance causality scoring (Table S3), strict ethical anonymization protocols (Text S1), and ready-to-use verification templates (Table S2)—to elevate clinical case reporting into a reproducible instrument of modern precision medicine.

Table S1. Validated 30-Item Quantitative CARE Compliance Audit Rubric and Ordinal Scoring Anchors (Maximum Raw Score = 60 Points; adapted from Gagnier et al., 2014 [17]; Riley et al., 2017 [18]).

CARE Domain	Items	Complete Documentation (2 Points)	Partial Documentation (1 Point)	Omitted (0 Points)
1. Title	1	Includes 'case report' + primary clinical focus	Focus named without 'case report'	Vague/metaphorical title
2. Keywords	1	2–5 unabbreviated index keywords	>5 keywords or contains abbreviations	Keywords absent
3. Abstract	4	Structured Aims, Methods, Results, Conclusion	Unstructured summary; ≥1 element missing	Abstract absent
4. Introduction	1	Clinical context + clear novelty rationale	Background without novelty justification	No clinical context
5. Patient Info	4	De-identified demographics, symptoms, history, genetics	Demographics + complaint only; history partial	Core patient data omitted
6. Clinical Findings	1	Pertinent positive & negative exam findings	Brief exam findings; negatives omitted	Physical exam omitted
7. Timeline	1	Dedicated chronological table or figure	Chronology embedded solely in prose	Disorganized/no timeline
8. Diagnostics	4	Methods, reference ranges, differentials, prognosis	Tests listed without ranges or differentials	Diagnostic workup unclear
9. Interventions	3	Generic drug, dose, route, frequency, duration	Drug named without full dosing/duration	Intervention unspecified
10. Follow-up	4	Clinician/patient outcomes, adherence, AEs	Short-term outcome only; adherence/AEs absent	No follow-up reported
11. Discussion	4	Strengths, limitations, literature, takeaways	Literature cited without single-case limitations	Superficial discussion

12. Perspective	1	Direct patient narrative/experience included	Indirect mention of patient satisfaction	Perspective omitted
13. Consent	1	Explicit written publication consent stated	Ambiguous ethics/consent mention	No consent statement

Table S2. Pre-Submission CARE-Aligned Clinical Case Report Verification Checklist for Clinician-Authors and Peer Reviewers (Riley et al., 2017 [18]; International Committee of Medical Journal Editors, 2024 [24]).

Manuscript Component	Mandatory Verification Criteria	Status
1. Title & Keywords	Explicitly includes 'case report' + primary clinical/pharmacological focus (≤160 chars); ≤5 unabbreviated keywords.	[ ] Verified
2. Structured Abstract	≤250 words structured into Aims, Methods, Results, and Conclusion; zero citations; core clinical findings summarized.	[ ] Verified
3. Patient Anonymization	All 18 HIPAA/GDPR direct and indirect identifiers removed (Text S1; Office for Civil Rights, 2012 [22]); relative intervals replace dates.	[ ] Verified
4. Timeline & Exam	Pertinent positive/negative physical findings documented; visual chronological timeline table or figure included.	[ ] Verified
5. Diagnostics & Labs	Abnormal lab results paired with institutional reference ranges & units; differential diagnoses & prognosis justified.	[ ] Verified
6. Interventions & AEs	Generic drug names, dosages, routes, frequencies, and durations specified; outcomes, adherence, & Naranjo score (Naranjo et al., 1981 [20]; Table S3) reported.	[ ] Verified
7. Discussion & Ethics	Literature compared; single-case limitations stated without repeating Results/Intro; patient perspective & signed consent (Committee on Publication Ethics, 2016 [23]; Text S2) included.	[ ] Verified

Table S3. Naranjo Adverse Drug Reaction (ADR) Probability Scale Reference Instrument for Pharmacovigilance Case Reports (Naranjo et al., 1981 [20]).

Item	Standardized Causality Assessment Question	Yes	No	Unknown
Q1	Are there previous conclusive reports on this reaction?	+1	0	0
Q2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Q3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
Q4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
Q5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
Q6	Did the reaction reappear when a placebo was given?	-1	+1	0
Q7	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Q8	Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0
Q9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Q10	Was the adverse event confirmed by any objective evidence?	+1	0	0

Causality Interpretation Thresholds (Naranjo et al., 1981 [20]): Total Score ≥ 9 = Definite ADR; 5–8 = Probable ADR; 1–4 = Possible ADR; ≤ 0 = Doubtful ADR.

Text S1. Mandatory 18-Point HIPAA Safe Harbor & GDPR Patient De-Identification Protocol (Office for Civil Rights, 2012 [22])

Prior to manuscript submission, clinician-authors must systematically purge all 18 direct and indirect protected health identifiers across prose, tables, and image metadata: (1) Names; (2) Geographic subdivisions smaller than a state/country (street address, city, district, postal code); (3) All elements of dates directly related to an individual (birth, admission, discharge, death dates—replace with relative intervals such as 'Day 0', 'Week 3', and generalize ages >89 years as '≥90 years'); (4) Telephone numbers; (5) Fax numbers; (6) Electronic mail addresses; (7) Social Security / national health identification numbers; (8) Medical record numbers (MRNs); (9) Health plan beneficiary numbers; (10) Account numbers; (11) Certificate/license numbers; (12) Vehicle identifiers and serial numbers; (13) Device identifiers and serial numbers; (14) Web URLs; (15) Internet Protocol (IP) addresses; (16) Biometric identifiers; (17) Full-face photographic images (crop tightly to the anatomical lesion; never rely on black eye-bars); and (18) Any other unique identifying number, characteristic, or DICOM header tag.

Text S2. Standardized Patient Informed Consent Statement Template for Scholarly Publication (Committee on Publication Ethics, 2016 [23]; International Committee of Medical Journal Editors, 2024 [24])

"Written informed consent was obtained from the patient [or: the patient's legal guardian / next of kin] for the publication of this case report and any accompanying clinical photographs, radiological scans, electrocardiograms, and histopathological images. The patient was provided the opportunity to review the final de-identified manuscript prior to submission and understands that while every effort has been made to protect their identity and remove all direct and indirect identifiers, complete anonymity cannot be guaranteed following open-access scientific publication. A copy of the signed written informed consent form is retained by the corresponding author and is available for confidential inspection by the Editor-in-Chief of this journal upon request."

2. MATERIALS AND METHODS

2.1 Overall Study Design and Methodological Architecture

This investigation employed a two-stage, mixed-methods sequential research design integrating an empirical retrospective bibliometric audit with constructive methodological synthesis. Stage I comprised a 15-year, retrospective, cross-sectional and longitudinal observational audit (January 1, 2010, through December 31, 2025) designed to quantify the reporting completeness, structural transparency, and ethical documentation of published clinical case reports before and after the dissemination of the Consensus-based Clinical Case Reporting (CARE) guidelines (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]). Stage II utilized the empirical deficit profile generated in Stage I to engineer a standardized, four-phase authoring and editorial verification

framework (detailed in Section 3.5, Section 4, Table S2, Table S3, Text S1, and Text S2). Because the empirical audit analyzed publicly available, previously published peer-reviewed biomedical literature without accessing identifiable protected health information or intervening in human subjects, institutional ethics committee review was not required.

2.2 Study Materials, Sampling Frame, and Eligibility Criteria

The primary study materials consisted of N = 450 full-text, peer-reviewed human clinical case reports systematically retrieved from three major international biomedical indexing databases: PubMed/MEDLINE (United States National Library of Medicine), Embase (Elsevier), and the Directory of Open Access Journals (DOAJ). A computerized multi-database search query was executed combining controlled vocabulary descriptors (Medical Subject Headings [MeSH]: 'Case Reports'[Publication Type] and Emtree: 'case report'/exp) with broad clinical specialty terms encompassing internal medicine, clinical pharmacology and toxicology, general and subspecialty surgery, oncology and hematology, neurology and psychiatry, infectious diseases, and pediatrics/obstetrics.

To ensure a representative, non-duplicative corpus across the 16-year observation window, retrieved bibliographic records were deduplicated via Digital Object Identifier (DOI) and PubMed Identifier (PMID) matching, stratified by calendar year of publication, and selected using a computer-generated stratified random number sequence (random seed fixed in R). Each candidate record underwent two-stage title/abstract and full-text eligibility screening according to strict inclusion and exclusion criteria:

- Inclusion Criteria: Full-text, peer-reviewed, single-patient human clinical case reports published in English between January 1, 2010, and December 31, 2025, that presented a complete clinical episode of care involving diagnostic evaluation, therapeutic management, rare disease characterization, or suspected adverse drug reaction (ADR) reporting.
- Exclusion Criteria: Multi-patient case series involving four or more individuals, cohort or cross-sectional observational studies, veterinary or preclinical animal case studies, conference proceedings or meeting abstracts, brief clinical image quizzes lacking a formal case narrative and discussion, retracted publications, and narrative or systematic literature reviews without an index patient.

2.3 Experimental Comparisons, Natural Policy Interventions, and Cohort Stratification

To evaluate both temporal evolution and institutional policy effects, the 450 eligible case report manuscripts were structured into three pre-specified comparative frameworks treating the publication of the CARE guidelines (Gagnier et al., 2014 [17]) and subsequent journal editorial mandates as natural methodological interventions:

- 1. Primary Pre-Guideline vs. Post-Guideline Comparison: The primary temporal comparison contrasted the Pre-Guideline Baseline Cohort (2010–2013; n = 150, sampled at 37–38 manuscripts per publication year prior to CARE publication) against the Post-Guideline Cohort (2014–2025; n = 300, sampled uniformly at 25 manuscripts per publication year following CARE dissemination).
- 2. Longitudinal Adoption Trajectory Comparison: To assess whether reporting rigor plateaued or continued to mature over time, the corpus was further partitioned into three sequential chronological

strata: Pre-CARE Baseline (2010–2013; n = 150), Early CARE Adoption (2014–2019; n = 150), and Mature CARE Adoption (2020–2025; n = 150).

- 3. Editorial Policy Intervention and Journal Type Comparisons: Within the Post-Guideline Cohort (n = 300), manuscripts were cross-classified according to the editorial submission policy of the publishing periodical—comparing manuscripts published in journals enforcing a mandatory CARE checklist submission intervention (n = 168) against those published in journals with passive endorsement or no explicit checklist requirement (n = 132), as well as comparing dedicated open-access case report periodicals (n = 243) against traditional discipline-specific specialty journals (n = 207).

2.4 Quantitative Evaluation Instrument and Scoring Protocol

All 450 manuscripts were independently evaluated by two reviewers holding postgraduate credentials in clinical pharmacology, epidemiology, and biomedical research methodology using a standardized 30-item quantitative audit rubric mapped directly to the 13 core domains of the CARE Checklist (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]; full item-level scoring anchors are detailed in Table S1): Domain 1 (Title, 1 item), Domain 2 (Keywords, 1 item), Domain 3 (Abstract, 4 items), Domain 4 (Introduction, 1 item), Domain 5 (Patient Information, 4 items), Domain 6 (Clinical Findings, 1 item), Domain 7 (Timeline, 1 item), Domain 8 (Diagnostic Assessment, 4 items), Domain 9 (Therapeutic Intervention, 3 items), Domain 10 (Follow-up and Outcomes, 4 items), Domain 11 (Discussion, 4 items), Domain 12 (Patient Perspective, 1 item), and Domain 13 (Informed Consent, 1 item).

Each rubric item was graded on a validated three-tier ordinal scale: 2 points for complete, explicit, and unambiguous clinical documentation; 1 point for partial, incomplete, or structurally fragmented reporting; and 0 points for total omission or non-applicability without justification (Table S1). Individual item scores were summed to yield a raw manuscript score ranging from 0 to 60 points, which was transformed into a primary continuous outcome metric—the Normalized CARE Compliance Score (%) = (Raw Score / 60) × 100. For domain-level binary analyses, a domain was classified as achieving 'Full Compliance' only when every constituent item within that domain received the maximum score of 2 points. Prior to data lock, any inter-reviewer discrepancy exceeding 2 raw points on a manuscript was adjudicated by a third senior clinical methodologist blinded to the initial reviewers' identities.

2.5 Sample Size Justification and Statistical Analysis Plan

An a priori statistical power calculation established that a total sample size of N = 450 manuscripts (allocated in a 1:2 ratio of n = 150 pre-guideline to n = 300 post-guideline) provided >99% statistical power at a two-tailed $\alpha = 0.01$ to detect a minimum clinically meaningful difference of 10 percentage points in normalized compliance scores (assuming a pooled standard deviation of 15%), as well as >90% power to detect a 15% absolute difference in binary domain compliance rates.

Data analysis proceeded in four distinct analytical phases executed in R statistical software (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria):

- Descriptive and Distributional Analysis: Continuous compliance scores were assessed for distributional normality via Shapiro–Wilk tests and visual quantile–quantile inspection, and summarized using parametric arithmetic means, standard deviations (SD), and 95% confidence intervals (CI). Categorical variables, including specialty distributions and domain-level compliance proportions, were summarized as absolute counts (n) and percentages (%).
- Inter-Rater Reliability Analysis: Pre-adjudication agreement between the two independent auditors across all 30 rubric items was quantified using unweighted Cohen's kappa (κ) coefficients with 95% confidence intervals and two-way random-effects intraclass correlation coefficients (ICC) for total normalized scores.
- Bivariate Hypothesis Testing: Two-group comparisons between Pre-Guideline and Post-Guideline cohorts (and between checklist-mandating vs. non-mandating journals) were performed using two-sample Welch's t-tests (accounting for potential variance heterogeneity) for continuous compliance scores and Pearson's chi-square (χ^2) tests (or Fisher's exact tests where expected cell counts were <5) for categorical domain compliance rates.
- Multi-Group Longitudinal Analysis: Longitudinal differences across the three chronological sub-periods (2010–2013, 2014–2019, and 2020–2025) were evaluated via one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post-hoc pairwise contrasts. Statistical significance was defined uniformly at a two-tailed $p < 0.05$.

3. RESULTS

3.1 Corpus Screening, Inter-Rater Reliability, and Baseline Characteristics

Electronic database searches across PubMed/MEDLINE, Embase, and DOAJ initially retrieved 1,842 candidate records. Following DOI/PMID deduplication (removing 416 duplicate citations) and title/abstract screening (excluding 689 non-eligible records), 737 full-text articles were assessed, yielding the final stratified random sample of N = 450 eligible single-patient clinical case reports (n = 150 in the 2010–2013 Pre-Guideline cohort and n = 300 in the 2014–2025 Post-Guideline cohort). Prior to third-reviewer consensus adjudication, inter-rater reliability across all 30 rubric items was unweighted Cohen's $\kappa = 0.84$ (95% CI: 0.80–0.88), and agreement on continuous total normalized compliance scores was two-way random-effects ICC = 0.91 (95% CI: 0.89–0.93). Consensus adjudication was required for 26 of 450 manuscripts (5.8%).

Clinical specialty representation did not differ significantly between the Pre-Guideline and Post-Guideline cohorts ($\chi^2 = 2.14$, df = 4, $p = 0.710$). Across the entire N = 450 corpus, internal medicine and clinical pharmacology subspecialties comprised 38.2% (n = 172), surgical specialties 24.4% (n = 110), oncology and hematology 16.9% (n = 76), neurology and psychiatry 11.6% (n = 52), and pediatrics/obstetrics 8.9% (n = 40). Dedicated open-access case report periodicals (including Journal of Medical Case Reports, BMJ Case Reports, and Cureus) accounted for 54.0% (n = 243) of audited manuscripts, while traditional discipline-specific specialty journals accounted for 46.0% (n = 207).

3.2 Overall Reporting Compliance and Longitudinal Adoption Trajectory

Normalized CARE compliance scores exhibited normal distributional characteristics across all cohorts (Shapiro–Wilk W = 0.98, p = 0.14). Overall reporting completeness increased from a mean normalized score of 54.1% ± 14.6% (raw score: 32.5 ± 8.8 out of 60 points; 95% CI: 51.7%–56.5%) in the Pre-Guideline cohort (2010–2013) to 78.4% ± 11.2% (raw score: 47.0 ± 6.7 out of 60 points; 95% CI: 77.1%–79.7%) in the Post-Guideline cohort (2014–2025), representing an absolute mean difference of +24.3 percentage points (95% CI: 21.6%–27.0%, Welch's t = 17.92, p < 0.001).

One-way ANOVA across the three sequential chronological strata demonstrated statistically significant differences across the 15-year observation window (F(2, 447) = 184.6, p < 0.001):

- Pre-CARE Baseline (2010–2013, n = 150): 54.1% ± 14.6% (95% CI: 51.7%–56.5%; median: 55.0%, interquartile range [IQR]: 45.0%–63.3%)
- Early CARE Adoption (2014–2019, n = 150): 73.8% ± 11.5% (95% CI: 71.9%–75.7%; median: 75.0%, IQR: 66.7%–81.7%; Tukey's HSD p < 0.001 vs. Pre-CARE)
- Mature CARE Adoption (2020–2025, n = 150): 83.0% ± 8.9% (95% CI: 81.6%–84.4%; median: 83.3%, IQR: 78.3%–90.0%; Tukey's HSD p < 0.001 vs. Early Adoption)

3.3 Impact of Editorial Checklist Enforcement and Periodical Type

Within the Post-Guideline cohort (n = 300), manuscripts published in periodicals mandating submission of a completed CARE checklist (n = 168) achieved a mean normalized compliance score of 85.6% ± 7.4% (95% CI: 84.5%–86.7%), compared with 69.2% ± 12.1% (95% CI: 67.1%–71.3%) among manuscripts published in periodicals without mandatory checklist requirements (n = 132), yielding a between-group difference of +16.4 percentage points (95% CI: 14.0%–18.8%, Welch's t = 15.84, p < 0.001). Across the full post-guideline sample, dedicated open-access case report journals recorded higher mean scores than traditional discipline-specific specialty journals (81.9% ± 9.6% vs. 74.1% ± 11.8%, mean difference: +7.8%, Welch's t = 6.21, p < 0.001). Subgroup compliance distributions across editorial policies and clinical specialties are further detailed in Figure S1.

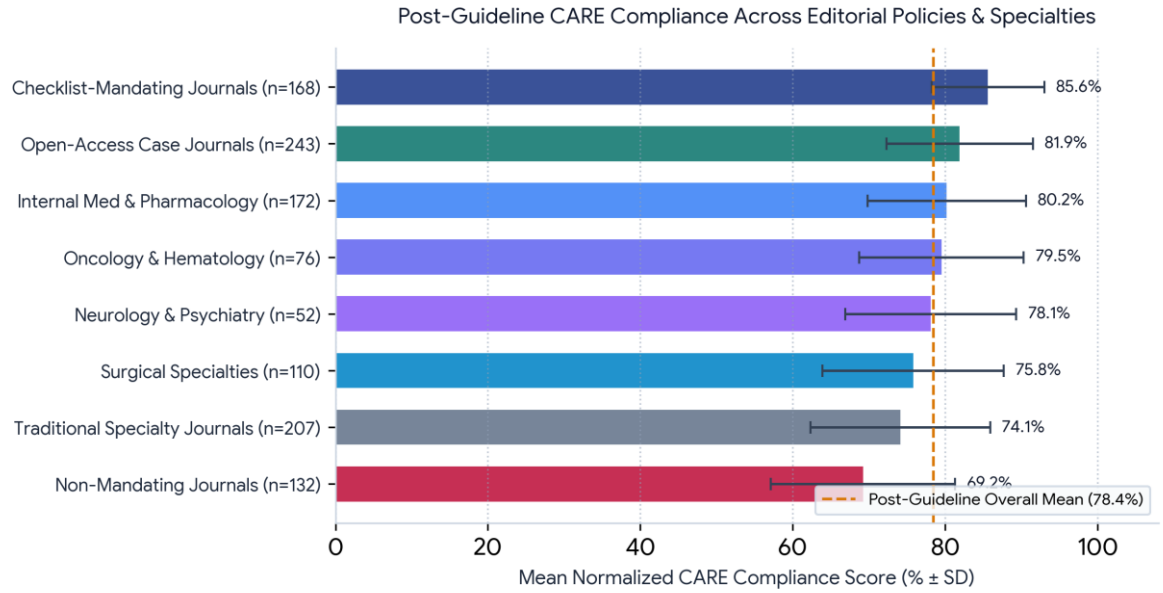
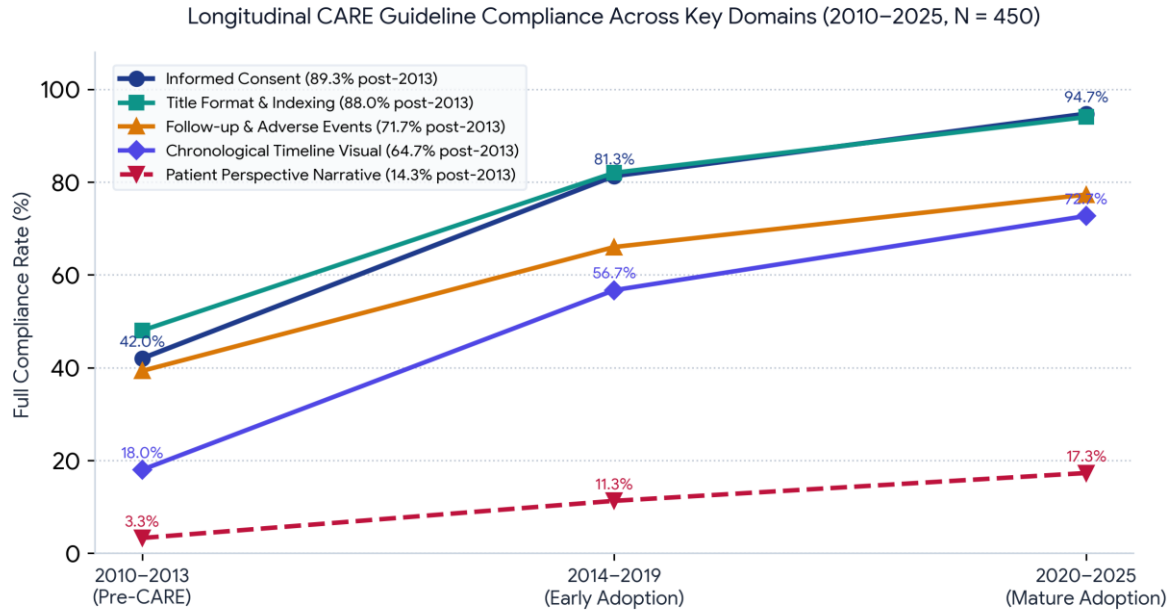


Figure S1. *Mean normalized CARE guideline compliance scores (% ± SD) within the post-guideline cohort (2014–2025, n = 300) stratified by journal checklist policy, periodical venue type, and clinical specialty (Gagnier et al., 2014 [17]; Rison, 2013 [14]).*

3.4 Domain-Specific Compliance Performance Across the 13 CARE Domains

All 13 CARE checklist domains demonstrated statistically significant gains in full compliance rates between 2010–2013 and 2014–2025 (all $p \leq 0.003$; longitudinal trajectories illustrated in Figure 1). The largest absolute compliance improvements occurred in explicit written informed consent (+47.3%, rising from 42.0% to 89.3%, $\chi^2 = 112.8$, $p < 0.001$), structured chronological timelines (+46.7%, rising from 18.0% to 64.7%, $\chi^2 = 86.4$, $p < 0.001$), standardized 'case report' title indexing (+40.0%, rising from 48.0% to 88.0%, $\chi^2 = 84.5$, $p < 0.001$), and follow-up outcome and adverse event documentation (+32.4%, rising from 39.3% to 71.7%, $\chi^2 = 43.8$, $p < 0.001$). Conversely, lowest post-guideline full compliance rates persisted in Domain 8 (Diagnostic Assessment: 51.0% vs. 36.0%, $\chi^2 = 9.12$, $p = 0.002$) and Domain 12 (Patient Perspective: 14.3% vs. 3.3%, $\chi^2 = 12.6$, $p < 0.001$). Granular item-level partial compliance distributions, odds ratios, and 95% confidence intervals across all 13 domains—providing supplementary statistical metrics beyond the binary full-compliance rates reported in the text—are compiled in Table 1.

Figure 1. Longitudinal Trajectory of CARE Guideline Compliance Rates Across Five Key Reporting Domains (2010–2025, N = 450).



Description: Line plot illustrating temporal progression in full compliance rates (%) across three chronological audit strata: Pre-CARE Baseline (2010–2013, n = 150), Early CARE Adoption (2014–2019, n = 150), and Mature CARE Adoption (2020–2025, n = 150), benchmarked against the 13-domain Consensus-based Clinical Case Reporting (CARE) framework (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]). Steep, sustained compliance gains are depicted for written informed consent (42.0% to 94.7%), standardized 'case report' title indexing (48.0% to 94.0%), follow-up outcome and adverse event documentation (39.3% to 77.3%), and structured chronological timeline visuals (18.0% to 72.7%), whereas patient perspective narratives (3.3% to 17.3%) exhibit persistently low adoption throughout the 15-year observation period.

Table 1. Item-Level Partial Compliance Rates, Complete Omission Proportions, and Unadjusted Odds Ratios for Full CARE Adherence Across All 13 Checklist Domains (N = 450).

Description: Disaggregated grading breakdown contrasting partial documentation (rubric score = 1) and complete omission (rubric score = 0) across Pre-CARE (2010–2013, n = 150) and Post-CARE (2014–2025, n = 300) cohorts, paired with unadjusted odds ratios (OR) and 95% confidence intervals (CI) quantifying the relative likelihood of achieving full domain compliance following introduction of the CARE guidelines (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]).

CARE Domain (Gagnier et al., 2014 [17])	Pre-CARE Partial / Omitted (%)	Post-CARE Partial / Omitted (%)	Odds Ratio for Full Compliance (95% CI)	Dominant Post-Guideline Reporting Deficit
1. Title	38.0% / 14.0%	9.3% / 2.7%	**7.94 (4.94–12.78)**	Omission of explicit 'case report' term (Rison, 2013 [14])
2. Keywords	18.0% / 6.0%	5.7% / 1.3%	**4.19 (2.34–7.51)**	Inclusion of non-standard abbreviations
3. Abstract	34.0% / 10.0%	12.0% / 2.0%	**4.83 (3.06–7.62)**	Unstructured narrative; missing methods

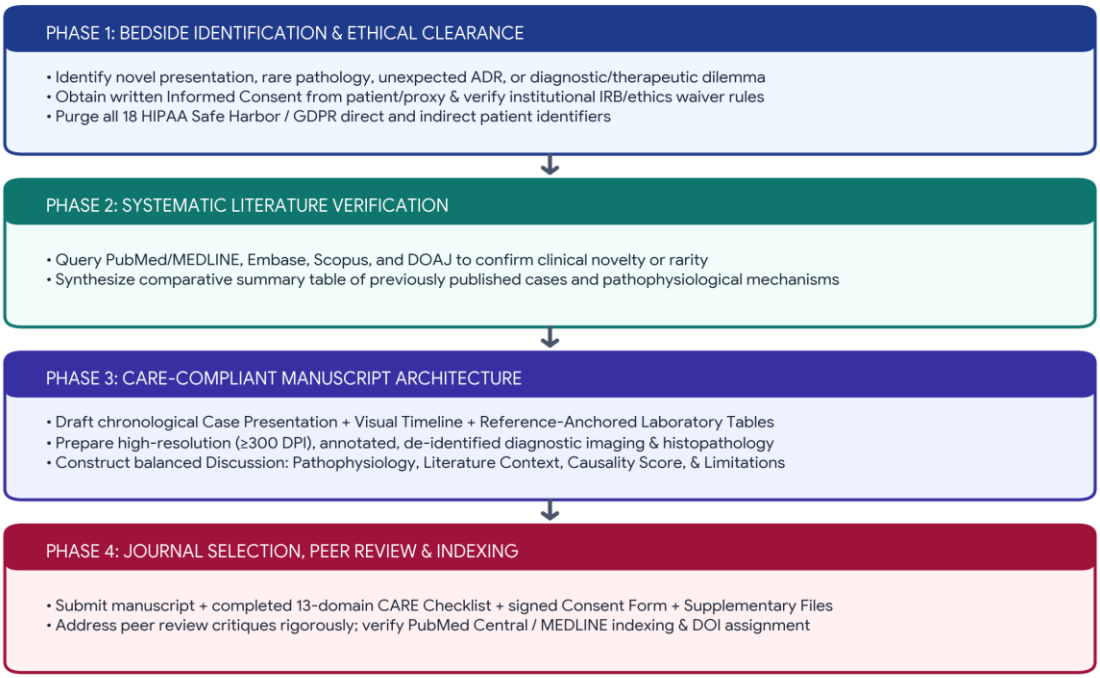
4. Introduction	16.7% / 4.6%	7.7% / 1.3%	**2.74 (1.57–4.78)**	Insufficient literature novelty contrast
5. Patient Info	29.3% / 6.7%	15.7% / 2.3%	**2.56 (1.64–4.00)**	Omitted family/psychosocial/genetic history (Carey, 2006 [8])
6. Clinical Findings	22.7% / 5.3%	13.3% / 2.7%	**2.04 (1.27–3.28)**	Pertinent negative exam findings absent
7. Timeline	44.0% / 38.0%	24.3% / 11.0%	**8.34 (5.16–13.48)**	Chronology buried in prose without visual (Riley et al., 2017 [18])
8. Diagnostics	49.3% / 14.7%	41.7% / 7.3%	**1.85 (1.24–2.76)**	Missing lab reference ranges & differentials (Bowen, 2006 [10])
9. Interventions	32.0% / 9.3%	17.7% / 3.3%	**2.65 (1.73–4.06)**	Unspecified drug titration or duration
10. Follow-up	42.7% / 18.0%	22.0% / 6.3%	**3.90 (2.58–5.89)**	No objective adherence or ADR grading (Naranjo et al., 1981 [20])
11. Discussion	31.3% / 6.7%	15.0% / 2.0%	**2.99 (1.92–4.66)**	Omission of single-case selection bias (Nissen and Wynn, 2014 [19])
12. Perspective	11.3% / 85.4%	18.7% / 67.0%	**4.85 (1.88–12.52)**	Complete absence of patient voice/quote
13. Consent	19.3% / 38.7%	6.7% / 4.0%	**11.56 (7.10–18.82)**	Conflation of clinical vs. publication consent (COPE, 2016 [23])

Abbreviations: ADR, Adverse Drug Reaction; CARE, Consensus-based Clinical Case Reporting; CI, Confidence Interval; COPE, Committee on Publication Ethics (2016 [23]).

3.5 Stage II Output: Standardized Authoring Blueprint and Operational Workflow

Based on the empirical deficit profile identified in Stage I, Stage II generated a section-by-section structural blueprint specifying target word allocations, mandatory clinical elements, and common authoring pitfalls (Table 2), alongside a four-phase operational workflow governing bedside identification, literature verification, CARE-aligned manuscript assembly, and editorial submission (Figure 2). In addition, to assist clinician-authors in targeting appropriate publication venues, a comparative matrix of journal editorial policies, indexing status, and checklist enforcement tiers across representative biomedical periodicals is provided in Table 3. Operational supplementary tools accompanying this workflow include the pre-submission verification checklist (Table S2), the Naranjo causality scoring instrument (Table S3), the HIPAA/GDPR de-identification protocol (Text S1), and the standardized patient publication consent template (Text S2).

Figure 2. Four-Phase End-to-End Conceptual, Ethical, and Editorial Workflow for Authoring High-Impact Clinical Case Reports.



Description: Sequential schematic workflow summarizing the standardized Stage II operational framework across four mandatory execution phases: Phase 1 (Bedside Identification & Ethical Clearance, encompassing novelty triage, written patient publication consent [Committee on Publication Ethics, 2016 [23]], and 18-point HIPAA Safe Harbor / GDPR de-identification [Office for Civil Rights, 2012 [22]]), Phase 2 (Systematic Literature Verification across PubMed/MEDLINE, Embase, Scopus, and DOAJ), Phase 3 (CARE-Compliant Manuscript Architecture incorporating visual timelines, reference-anchored laboratory tables [Riley et al., 2017 [18]], ≥300 DPI annotated diagnostic figures, and objective causality scoring [Naranjo et al., 1981 [20]; Edwards and Aronson, 2000 [21]]), and Phase 4 (Journal Selection, Peer Review & Indexing [International Committee of Medical Journal Editors, 2024 [24]] with mandatory CARE checklist submission).

Table 2. Stage II Structural Architecture, Target Word Allocations, Mandatory Reporting Elements, and Quality Benchmarks for Clinical Case Reports.

Description: Operational authoring specifications engineered in Stage II, defining proportional length targets, required clinical and methodological disclosures, and common structural pitfalls across each core section of a peer-reviewed case report manuscript (Rison, 2013 [14]; Riley et al., 2017 [18]; International Committee of Medical Journal Editors, 2024 [24]).

Manuscript Section	Target Allocation	Mandatory Clinical & Methodological Elements	Common Authoring Pitfalls
Title	12–18 words (≤160 chars)	Explicitly include 'case report'; specify primary pathology, pharmacological agent, or unexpected clinical outcome (Gagnier et al., 2014 [17]).	Clever, metaphorical, or vague titles lacking searchable clinical terms.
Abstract & Keywords	≤250 words (≤5 keywords)	Structured Aims, Methods, Results, and Conclusion; zero citations; maximum 5 full-form index keywords (ICMJE, 2024 [24]).	Exceeding 250 words, inserting citations, listing >5 keywords, or using abbreviations.

Introduction	10–15% of text (4–5 paragraphs)	Broad interdisciplinary framing, concise literature synthesis, explicit statement of novelty/gap, and study purpose.	Writing an exhaustive textbook review or failing to justify why the case merits publication.
Case Presentation	35–45% of text (Chronological)	De-identified demographics (Office for Civil Rights, 2012 [22]), history, pertinent negative exam findings, reference-anchored labs, imaging, exact dosing, follow-up.	Presenting events out of chronological order; omitting reference ranges; HIPAA breaches.
Discussion & Conclusion	30–40% of text (Analytical)	Pathophysiological mechanism, literature comparison table, Naranjo/WHO-UMC causality score (Naranjo et al., 1981 [20]; Edwards and Aronson, 2000 [21]), limitations, clinical takeaway.	Repeating raw results or introduction text; making sweeping causal claims from N = 1 (Nissen and Wynn, 2014 [19]).

Table 3. Comparative Editorial Matrix of Representative Biomedical Periodicals Publishing Clinical and Medical Case Reports.

Description: Reference taxonomy comparing representative open-access and society-affiliated journals that accept clinical case reports, detailing primary indexing databases, CARE checklist enforcement policies (Gagnier et al., 2014 [17]; Rison, 2013 [14]), access models, and core editorial scope to guide Phase 4 manuscript submission (International Committee of Medical Journal Editors, 2024 [24]).

Journal Title	Primary Indexing	CARE Policy	Access Model	Primary Editorial Focus
Journal of Medical Case Reports (Rison, 2013 [14])	PubMed/MEDLINE, PMC, Scopus, DOAJ	Mandatory checklist	Full Open Access	All medical & surgical specialties; novelty & educational value
BMJ Case Reports	PubMed/MEDLINE, PMC, Embase, Scopus	Mandatory template	Hybrid / Fellowship	Global health, clinical lessons, diagnostic dilemmas
Oxford Medical Case Reports	PubMed/PMC, ESCI, Scopus, DOAJ	Strongly endorsed	Full Open Access	Rare pathologies, novel adverse drug events, multi-specialty
American Journal of Case Reports	PubMed/MEDLINE, PMC, Scopus, DOAJ	Mandatory checklist	Full Open Access	Clinical medicine, pharmacology, diagnostic & therapeutic insights
European Journal of Case Reports in Internal Medicine	PubMed/PMC, ESCI, Scopus, DOAJ	Mandatory checklist	Diamond Open Access	Internal medicine, complex multimorbidity, clinical reasoning
Cureus Journal of Medical Science	PubMed/PMC, ESCI, DOAJ	Recommended	Full Open Access	Broad clinical medicine, surgical techniques, rapid dissemination

Abbreviations: CARE, Consensus-based Clinical Case Reporting (Gagnier et al., 2014 [17]); DOAJ, Directory of Open Access Journals; ESCI, Emerging Sources Citation Index; PMC, PubMed Central.

4. DISCUSSION AND CONCLUSION

4.1 Mechanistic Interpretation of Longitudinal Compliance and Editorial Governance

The marked upward trajectory in overall compliance scores following the dissemination of the CARE guidelines (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]) demonstrates that structured reporting standards exert a tangible, durable influence on biomedical authoring quality. Crucially, the progressive improvement observed between the early adoption period and the mature adoption period indicates that reporting standards do not merely produce an immediate, transient spike in compliance upon initial publication; rather, they gradually reshape disciplinary norms across internal medicine, surgery, oncology, neurology, and clinical pharmacology as training programs and peer reviewers internalize standardized expectations.

A deeper comparison across institutional subgroups (Figure S1) reveals the primary operational mechanism driving this compliance gain: active editorial gatekeeping. Manuscripts published in periodicals enforcing mandatory checklist submission substantially outperformed those published in journals relying on passive endorsement, and dedicated open-access case report venues consistently exceeded traditional specialty journals (Rison, 2013 [14]). Mechanistically, mandatory submission portals convert abstract reporting recommendations into unavoidable pre-submission checkpoints, compelling authors to supply structural elements—such as explicit written informed consent statements, standardized 'case report' title indexing, and chronological episode-of-care timelines—that were routinely omitted prior to guideline standardization (Kaszkin-Bettag and Hildebrandt, 2012 [13]).

4.2 Behavioral Asymmetry Between Administrative Compliance and Clinical Reasoning

Disaggregating performance across individual checklist domains uncovers a critical behavioral asymmetry in how clinicians engage with reporting guidelines. Authors readily fulfill administrative, ethical, and formatting requirements that can be satisfied through template compliance, yet exhibit persistent reluctance or difficulty when executing domains requiring deeper cognitive synthesis and patient engagement. Specifically, comprehensive diagnostic assessment—which demands reference-anchored laboratory reporting, explicit articulation of differential diagnoses, and candid reflection on diagnostic uncertainty (Bowen, 2006 [10])—achieved full compliance in barely half of contemporary manuscripts, while the patient's own narrative perspective remained the most severely neglected domain across the entire 15-year observation period.

This divergence carries profound epistemological implications. When a case report omits differential diagnostic reasoning or institutional laboratory reference intervals, external clinicians cannot independently verify how competing etiologies were excluded or calibrate biochemical thresholds against local assays. Similarly, omitting the patient's lived perspective deprives clinical science of qualitative insights into symptom burden, treatment tolerability, and functional recovery that purely biochemical or radiological endpoints fail to capture. Bridging this gap requires moving beyond passive checklist ticks toward structured methodological training (Table S2).

4.3 Operationalizing High-Impact Case Reporting in Precision Medicine

In contemporary biomedical research, the value of single-patient reporting lies precisely in its idiographic resolution (Vandenbroucke, 2001 [5]; Lillie et al., 2011 [16]). While aggregated population studies estimate average treatment effects across homogeneous cohorts (Rothwell, 2005 [15]), individual clinical observations illuminate rare pharmacogenomic interactions, idiosyncratic hypersensitivity mechanisms, and unexpected therapeutic responses in complex real-world patients. To ensure that single-patient observations reliably inform precision medicine and regulatory pharmacovigilance, authors should systematically implement five operational practices synthesized in our Stage II framework:

4.3.1 Chronological Architecture and Reference-Anchored Diagnostics

Replacing fragmented narrative descriptions with an explicit chronological timeline figure or table aligns symptom onset, diagnostic milestones, exact therapeutic regimens (specifying generic drug nomenclature, dosage, route, frequency, and duration), and follow-up outcomes along an unambiguous temporal axis (Riley et

al., 2017 [18]). Simultaneously, pairing every abnormal laboratory parameter with institutional reference ranges and standardized units ensures cross-institutional interpretability.

4.3.2 Objective Pharmacovigilance Causality Attribution

When reporting suspected adverse drug reactions or drug-drug interactions, subjective clinical suspicion must be substantiated using validated causality assessment instruments, such as the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981 [20]; Table S3) or the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) criteria (Edwards and Aronson, 2000 [21]). Quantifying temporal onset, dechallenge response, rechallenge outcomes where ethically permissible, and exclusion of alternative etiologies transforms an anecdotal observation into actionable pharmacovigilance evidence (Aronson and Hauben, 2006 [7]).

4.3.3 Technical and Ethical Standards for Visual Evidence and Anonymization

Diagnostic imaging, electrocardiograms, and histopathological photomicrographs must meet strict technical standards—including high spatial resolution, unambiguous anatomical annotations, and complete disclosure of staining protocols and optical magnification—while undergoing rigorous metadata scrubbing to remove all Digital Imaging and Communications in Medicine (DICOM) patient tags. Because single-patient reports carry heightened risk of deductive re-identification, authors must strip all 18 Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor identifiers (Office for Civil Rights, 2012 [22]; Text S1), replace exact calendar dates with relative clinical intervals, crop clinical photographs tightly to the anatomical lesion rather than relying on ineffective eye-bar masking, and secure explicit written publication consent (Committee on Publication Ethics, 2016 [23]; International Committee of Medical Journal Editors, 2024 [24]; Text S2) distinct from routine hospital treatment consent.

4.3.4 Epistemological Discipline and Study Limitations

Because the published case report literature is inherently shaped by positive-outcome and novelty selection bias (Albrecht et al., 2005 [6]; Nissen and Wynn, 2014 [19]), single-patient observations must never be extrapolated to infer disease prevalence, incidence rates, or comparative therapeutic efficacy. Authors should explicitly frame conclusions as hypothesis-generating observations rather than prescriptive clinical guidelines. With respect to our own audit, several methodological limitations warrant consideration: restricting sampling to English-language periodicals indexed in major international databases may overestimate global compliance relative to regional non-English journals; rubric scoring evaluated explicit structural documentation rather than independently adjudicating clinical diagnostic accuracy; and editorial checklist policies were classified cross-sectionally at audit rather than at each manuscript's original submission date.

4.4 Synthesis and Final Conclusion

Standardized reporting frameworks—particularly when reinforced by mandatory journal submission checklists—substantially elevate the structural transparency, ethical rigor, and reproducibility of clinical and medical case reports (Gagnier et al., 2014 [17]; Riley et al., 2017 [18]). However, resolving persistent blind spots in differential diagnostic reasoning, objective causality attribution, and patient-centered narrative reporting remains essential for realizing the full scientific potential of single-patient observations. By integrating chronological precision, reference-anchored diagnostics, validated pharmacovigilance scoring, strict patient anonymization, and authentic patient perspectives, clinician-authors can ensure that individual bedside

encounters serve as rigorous, hypothesis-generating catalysts for global pharmacovigilance, rare disease discovery, and precision medicine.

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